Influence of COVID-19 vaccines on surgical practice

A rapid review commissioned by RACS

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Recommendations:

1. Identify the patient's COVID-19 and vaccine status prior to surgery to inform surgical management. Irrespective of vaccine status, ensure existing recommendations regarding personal protective equipment (PPE) and infection control methods are followed.

2. When possible, patients should be fully vaccinated against SARS-CoV-2 with their most recent dose at least 14 days before undergoing an elective surgical procedure. This enables reactogenicity symptoms and most adverse events to be identified and resolved prior to surgery, as well as ensuring that patients are immune to SARS-CoV-2 thus minimising transmission and any potential complications. Further, any postoperative symptoms or complications can be correctly attributed to the vaccine or surgery.

3. Clinical guidance on adverse events causal to COVID-19 vaccines (e.g. anaphylaxis, thrombosis with thrombocytopenia and myocarditis/pericarditis) should be reviewed, as well as previous guidance on blood products and vaccination.

4. If patients present with an adverse event related to COVID-19 vaccines, it may be necessary to delay surgery until the patient has recovered or their condition stabilised.

5. Be aware that if the procedure occurs before the final vaccine dose, the patient is from a group known to have a poor immune response to vaccination, or the patient's vaccination status is unknown, the patient and operating staff are at greater risk of acquiring and transmitting SARS-CoV-2.

6. Urgent and emergency procedures should occur irrespective of vaccination status. Operating staff should be aware of the potential impact COVID-19 vaccination has on perioperative management. Vaccine-related adverse events are rare but can significantly impact surgical risk. Reactogenicity may mirror postoperative complications and patients and operative staff are at risk of acquiring and transmitting SARS-CoV-2.

7. Following surgery, it is recommended waiting at least 2 weeks before vaccinating. After major procedures the patient should also have returned to normal activity levels, or their condition should have stabilised before vaccinating (recommendation derived via consensus from working group).

Executive summary:

Introduction: COVID-19 vaccines are recommended for patients undergoing surgery. Vaccine-related reactogenicity and adverse events potentially complicate surgical management, therefore delaying elective surgery may aid in mitigating this risk. However, there is a lack of evidence-based guidance addressing these concerns. Therefore, the aims of this review are to determine the impact of vaccination on surgical management and identify an appropriate gap between receiving the COVID-19 vaccine and undergoing surgery.

Methods: A mixed methodology was used and consisted of a rapid review and input from a working group of clinicians. The rapid review entailed searching biomedical and preprint databases, and grey literature sites for relevant literature. Relevant studies were extracted, and the results synthesised narratively.

Results: If possible, separating COVID-19 vaccination and surgery by 2 weeks after the final COVID-19 vaccine dose is recommended as:

1. Most existing guidelines recommend a gap of at least 1 or 2 weeks between vaccination and surgery.
2. Reactogenicity (local and systemic adverse events) following COVID-19 vaccination was common, mild, transient, and typically resolved with a week.
3. Vaccine-related adverse events, including thrombosis with thrombocytopenia syndrome, myocarditis/pericarditis, and Guillain-Barre syndrome, were rare and generally occurred within 14 days of vaccination.
4. Immunity was achieved 7 to 14 days after the second dose of the COVID-19 vaccines.

Conclusion: For elective procedures, a 2 week gap between receiving the final (or booster) COVID-19 vaccine dose and surgery would enable the reactogenicity symptoms to resolve so that any postoperative symptom can be correctly attributed to the vaccine or surgery; allow most adverse events of special interest to emerge and be managed appropriately; and ensure patients are immunised to minimise transmission and spread of SARS-CoV-2. After major surgery, the patient should also have returned to normal activity levels or their conditioned stabilised before vaccinating.

For urgent and emergency procedures, operations should occur irrespective of vaccination status. However, if the patient has recently received the COVID-19 vaccine (or their vaccination status is unknown), operating staff need to be aware that reactogenicity manifests similarly to postoperative complications; vaccine-related adverse events can significantly impact surgical risk; and patients and operative staff are at risk of acquiring and transmitting SARS-CoV-2. It is paramount that surgical teams continue to follow best practice guidelines regarding COVID safe surgery.

Introduction

The COVID-19 pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has engendered substantive mortality and morbidity globally.[1,2] With no effective drug treatments approved,[3,4] health interventions have focused primarily on reducing viral transmission via barrier methods (e.g. social distancing and face masks) and vaccines.[5,6]

To date, 2 vaccines are used in Australia: the Pfizer/BioNTech (Comirnaty, BNT162b2) and the AstraZeneca vaccines (AZD1222, ChAdOx1).[7,8] The Janssen (Ad26.COV2.S) and Moderna (SpikeVax, mRNA-1273) vaccines have been granted provisional approval.[8] In Aotearoa New Zealand, the Pfizer vaccine is the only vaccine currently in use.[9] Both vaccines have promising efficacy, as inferred by the results of their phase II/III clinical trials.[10,11] However, the long-term safety of the vaccines is uncertain with reports linking the AstraZeneca vaccine to the emergence of thrombosis with thrombocytopenia syndrome (TTS), a syndrome characterised by blood clotting with low platelet counts.[7] Owing to the safety concern in younger age groups, the Australian Government recommended the use of the Pfizer vaccine to individuals under 60 years of age (i.e. those at higher risk of developing complications from AZD1222), with older adults recommended the AstraZeneca vaccine.[7] For higher-risk patient groups (e.g. immunocompromised) the appropriate vaccine is decided on a per case basis as vaccines may have reduced efficacy.[12]

Higher-risk patient groups, such as those undergoing surgery, are in urgent need of vaccination against COVID-19. Surgical patients are at risk of nosocomial acquisition of COVID-19 and perioperative COVID-19 increases the risk postoperative complications and mortality.[13-15] This risk may differ between those undergoing major or minor surgery. Irrespective of this, vaccinating patients prior to surgery reduces COVID-19-related complications and mortality postoperatively.[16] Thus, patients undergoing surgery should be prioritised to receive COVID-19 vaccines.[17]

Like surgery, vaccines place physiological stress on the body owing to the immunological response directed against the vaccine's epitopes.[18] However, the immediate reactogenicity, and the rare, but serious adverse events related to vaccines, may complicate surgical care. For example, the reactogenicity towards the COVID-19 vaccine and postoperative infections share similar symptoms (e.g. headache, fever, nausea) and the risk of TTS may influence how an operation, and postoperative recovery, is managed. Further, COVID-19 vaccines, including the Pfizer and AstraZeneca vaccines, require two doses for optimal effectiveness, hence recipients of these vaccines may remain at risk of acquiring COVID-19 following the initial dose. Thus, vaccine status is an important consideration when evaluating a patient's suitability for surgery. However, there is a lack of evidence-based guidance on the risks associated with, and when it is safe to, operate on a patient who has recently received a COVID-19 vaccine. There is also limited evidence regarding the risks of surgery on subsequent vaccination. Therefore, the overarching aims of this review are to determine an appropriate gap between COVID-19 vaccination and surgery, and to determine the impact of COVID-19 vaccination on surgical planning and care.

Methods

To address the aims of this review, a mixed methods approach was utilised and consisted of a rapid review and input from a working group of clinicians. Rapid reviews are streamlined systematic reviews that can be completed in shorter timeframes. It is a targeted approach that is narrower in scope, inclusion criteria and resources used.[19]

The working group consisted of immunologists, virologists, physicians, anaesthetists, and surgeons who provided clinical insight during the development of the protocol and drafting of the report.

Rapid review

The review was performed largely in accordance with the Preferred Reporting Items For Systematic Reviews and Meta-Analysis 2020 guidelines.[20]

Search strategy and study selection

Systematic searches of MEDLINE (via PubMed), medRxiv and bioRxiv were performed using a combination of medical subject headings and text terms relating to the population, intervention, comparator, and outcome criteria (PICO, ***Table 1***). The search terms were combined with methodological filters (e.g. adverse event[21] and systematic review filters[22]). Grey literature was also searched in accordance with the grey literature matters guidelines.[23] Regulatory agencies, medical societies and guideline repositories websites were the focus of grey literature searches. The reference list from relevant publications was also pearled to identify additional studies. For a complete list of the search strategy and terms used, refer to ***Appendix A***, ***Table 8***.

The search results were imported into a web application (Rayyan, Qatar Computing Research Institute, Al-Rayyan, Qatar)[24] with relevant studies identified by screening the title and abstracts, followed by reviewing their full text. Studies were included if they matched the PICO criteria. Relevant study information such as trial characteristics, patient demographics, vaccine manufacturer/doses and adverse events were extracted into a standardised template. Study selection and extraction was generally performed by a single researcher.

PICO criteria

The population of interest was adults and children eligible for a COVID-19 vaccine, and the intervention included all phase II/III completed COVID-19 vaccines (as of June 2021). The relevant vaccines were not limited to those approved in Australia/Aotearoa New Zealand given there is uncertainty which vaccines the Governments will use in the future or which vaccines clinicians will encounter in practice. The comparator, where applicable, was the absence of COVID-19 vaccine or placebo vaccine. Outcomes of interest included the serological response toward COVID-19 vaccines, vaccine-related reactogenicity (local and systemic adverse events) and vaccine-related adverse events (adverse events of special interest [AESI]). Several organisations have identified specific AESI that may be of relevance to COVID-19 vaccines because they are associated with other vaccines, specific vaccine platforms, or are events associated with COVID-19. To determine which AESI were relevant to the COVID-19 vaccine and surgery, the Brighton Collaboration list of AESI was used.[25] This is the focus of vaccine safety monitoring in Australia (TGA) and Aotearoa New Zealand (Medsafe), noting the list also

contains adverse events that are not relevant to surgical practice and potentially unrelated to the COVID-19 vaccine. Attempts were made to source information for all AESI listed by the Brighton Collaboration. However, AESI that were causally related to a COVID-19 vaccine and those most relevant to surgery were the focus. Comparative and non-comparative studies were included. Narrative reviews, letters, editorials, non-human studies, and non-English publications were excluded.

Table 1 PICO framework for research questions

Population	All populations
Intervention	COVID-19 vaccines (e.g. Comirnaty, AZD1222, mRNA-1273, Sputnik V)
Comparator	No vaccine or placebo
Outcomes	Serological response (e.g. SARS-CoV-2 IgG response, neutralising antibody) Reactogenicity (local and systemic adverse events, e.g. injection site pain, nausea) Adverse events of special interest (e.g. TTS, myocarditis/pericarditis)
Study design	Comparative (RCTs, non-RCTs, cohort studies) and non-comparative studies (single-arm trials, case series and reports)
Exclusion criteria	Narrative reviews, letters, editorials, non-human studies, and non-English publications

Abbreviations

PICO = population, intervention, comparator, outcomes, **RCTs =** randomised controlled trials, **TTS** = thrombosis with thrombocytopenia syndrome.

Analysis plan

To determine an appropriate delay between vaccination and surgery, the following factors were considered: existing guidelines; the type, duration, and severity of vaccine-related reactogenicity and AESI; and the immunological response towards a COVID-19 vaccine. When identifying relevant studies to address each section, the PICO criteria was broadly followed. However, each section utilised a slightly different evidence base owing to the type and volume of available literature. For example, grey literature (mostly medical association websites) was used to inform existing guidelines; RCTs, case series and results from vaccine safety surveillance databases were used to inform vaccine-related reactogenicity, AESI and the immunological response towards COVID-19 vaccines.

To frame the incidence and risk associated with AESI, the background rate of AESI was sourced (see Li [2021][26]). The background incidence reflects the number of AESI events per year in the general population and is used to inform the baseline risk of encountering the event in practice. To aid with the interpretation, the incidence of AESI was stratified using the Council for International Organizations of Medical Sciences (CIOMS) thresholds: very common (≥1/10 events per year), common (<1/10 to ≥1/100 events per year), uncommon (<1/100 to ≥1/1,000 events per year), rare (<1/1,000 to ≥1/10,000 events per year), and very rare (<1/100,000 events per year). To determine the incidence of AESI post-vaccination, regulatory agencies and safety surveillance databases were searched for AESI reported following COVID-19 vaccination. The total number of events and incidence per 100,000 doses was calculated because the number of vaccine recipients was infrequently

reported. Events were not annualised given the uncertainty in extrapolating the number of events out to a year. Importantly, many of the reported AESI were not clinically verified, and different databases were utilised in ascertaining rates compared to the background rate. Therefore, the incidence of AESI post-vaccination can only highlight which events have been observed and their relative frequency.

Results from included studies were extracted and synthesised narratively. Where there was sufficient evidence, the results were stratified by surgery type (elective/urgent and emergency, speciality area, and major/minor surgeries), vaccine manufacturer (e.g. AstraZeneca, Pfizer/BioNTech, Novavax) and risk groups.

Results

Existing recommendations and guidelines for COVID-19 vaccination and surgery

Summary

- Eighteen guidance documents were identified, of which two were peer reviewed. Most guidance documents did not explicitly state how the guidance was developed or whether the delay to surgery followed the first or second vaccine dose.
- For elective procedures, most guidance documents recommended separating vaccination and surgery by at least 1 or 2 weeks.
- For urgent and emergency procedures, a guidance document recommended the operation occur irrespective of vaccination status.

Results

Guideline databases, regulatory agencies and medical association websites were searched for existing recommendations and guidelines on when it is safe to operate following the COVID-19 vaccine or any other vaccine (***Appendix A***, ***Table 11***). Fourteen COVID-19-specific and four general vaccine guidance documents were identified from the literature (***Table 2***). The guidance documents were published by anaesthetists and surgical societies (k = 7), medical societies (k = 3), regulatory agencies (k = 4), health service providers (k = 2) and research institutes (k = 2) from Australia and New Zealand (k = 8), Europe (k = 6) and North America (k = 4). Two guidance documents were published in peer-reviewed journals. For the remaining guidance documents, it was unclear whether they were peer reviewed as they were published on the organisation's website. It was generally unclear how the recommendations were developed; when the methodology was stated, they involved a mix of expert opinion/review and literature search. Most guidance documents provided evidence on when to vaccinate prior to surgery (k = 15), with fewer studies providing guidance on when to vaccinate after the operation (k = 12). Two guidance documents addressed paediatric patients,[27-29] three were for specific indications (cancer or transplant surgery)[30-32] and the remaining documents did not specify the patient population. Five documents specified the delay related to elective procedures,[29,33-36] four documents related to major surgery[29,30,37,38] and one to emergency surgery.[36] The remaining did not specify surgery type.

<u>COVID-19 vaccines</u>

Preoperatively, most guidance documents recommended separating COVID-19 vaccination and surgical procedures by at least 1 or 2 weeks (k = 12).[31-35,37-43] Specifically, the guidance can be delineated into those recommending a delay of, less than 1 week (k = 3),[31,36,40] 1 week or more (k = 8),[31,33,34,37-41] and 2 weeks or more (k = 5).[32,35,40,42,43]

Postoperatively, most guidance documents recommended separating surgical procedures and COVID-19 vaccination by at least 1 week (k = 6).[30,33,34,37-39] A greater delay was required following transplant

surgery (1 to 3 months).[32] Other risk groups, such as patients with cancer, did not require extended delays beyond 1 or 2 weeks. There was no further information on high-risk patient groups.

It was infrequently reported whether the delay related to the first or final dose of COVID-19 vaccines. One guidance document noted surgical procedures should occur 2 weeks after the final dose of the vaccine,[42] and another document stated separating the vaccination and surgery by 1 week after the first or final dose.[33] When reported, the rationale for delaying vaccination or surgery was due to the overlap of symptoms between vaccine reactogenicity and postoperative complications (e.g. headache, fever, nausea).

For urgent and emergency operations, a guidance document noted the procedure should occur irrespective of COVID-19 vaccination status.[36]

General vaccines

For other vaccines, separating surgical procedures and vaccination was dependent on the type of vaccine (e.g. 2 days to 1 week for inactive vaccine, and 0 to 3 weeks for live attenuated vaccine)[27-29] and whether intravenous blood or immunoglobulin products were used during surgery (0 to 11 months).[44] It is unclear to what extent these recommendations are applicable to COVID-19 vaccines.

Table 2 Summary of existing guidelines and recommendation for separating COVID-19 vaccination and surgery

Organisation	Location	Pre-surgery recommendations	Post-surgery recommendations
COVID-19 vaccine guidance			
American Society of Anesthesiologists[42]	US	At least 2 weeks after final dose	NR
American Society of Transplantation [32]	US	At least 2 weeks pre-transplantation	1 to 3 months post-transplantation
Arthritis and Musculoskeletal Alliance (includes British Orthopaedic Association, British Society for Rheumatology and Rare Autoimmune Rheumatic Disease Alliance)[33]	UK	1 week between vaccination and surgery	1 week between vaccination and surgery
Association of Anaesthetists, Centre for Perioperative Care, The Federation of Surgical Specialty Associations, Royal College of Anaesthetists and Royal College of Surgeons of England[43]	UK	Several weeks before hospital admission	NR
Australasian Society of Aesthetic Plastic Surgeons ™ 39	Australia	≥1 week between vaccination and surgery	≥1 week between vaccination and surgery
Australasian Society of Clinical Immunology and Allergy[38]	Australia and Aotearoa New Zealand	1 week between vaccination and surgery	1 week between vaccination and surgery

Organisation	Location	Pre-surgery recommendations	Post-surgery recommendations
Australian Rheumatology Association[37]	Australia	≥1 week between vaccination and surgery	≥1 week between vaccination and surgery
Australian and New Zealand College of Anaesthetics[34]	Australia and Aotearoa New Zealand	≥1 week between vaccination and surgery	≥1 week between vaccination and surgery
Bowel Cancer Australia[30]	Australia	NR	1 to 2 weeks after surgery
COVID-19 Critical Intelligence Unit[40]	Australia	Few days to 3 to 4 weeks between vaccination and surgery	NR
Hospitals of Cologne[35]	Germany	15 days after the final dose	NR
National Cancer Control Programme [31]	Ireland	Ideal ≥1 week between vaccination and surgery, can be administered < 7 days before surgery	NR
Royal College of Surgeons of England[36]	UK	≤ 1 week between vaccination and surgery	NR
University Health Network[41]	Canada	≥1 week between vaccination and surgery	1 to 2 weeks after surgery
General vaccine guidance			
Association of Paediatric Anaesthetists of Great Britain and Ireland[28 29]	UK	2 days before surgery for inactivated virus vaccine, no delay for live attenuated virus vaccine	'No contraindication to vaccination immediately after surgery …'
Centre for Disease Control[45]	US	Not a contraindication to surgery	Not a contraindication
Department of Health[27]	Australia	1 week for inactive virus vaccine, 3 weeks for live attenuated vaccine	1 week after
Department of Health [a 44]	Australia	NR	Separate MMRV vaccine and use of blood or immunoglobulin products by 0–11 months

Abbreviations

MMRV = measles-mumps-rubella-varicella vaccine, **NR** = no recommendation, **UK** = United Kingdom, **US** = United States of America.

Notes

a = Guidance specific to measles-mumps-rubella, measles-mumps-rubella-varicella, or varicella vaccination. The interval is dependent on the type of products used. Following use of blood transfusion products, a delay of 0–6 months is recommended, for immunoglobulin products a delay of 3–11 months is recommended.

Recommendations

Elective procedures: Existing guidance documents recommend separating COVID-19 vaccination and surgical procedures by at least 1 or 2 weeks. The separation allows for symptoms to be correctly ascribed to the COVID-19 vaccine or the surgical procedure. Transplant recipients were recommended to delay vaccination 1 to 3 months post-operation. There was limited specific recommendations for other risk groups.

If blood or immunoglobulin products are used during surgery, patients may require a longer separation period between vaccination and surgery (based on existing guidance for the MMRV vaccine).

Urgent and emergency procedures: Existing guidance recommends that the operation proceed irrespective of vaccination status. However, vaccine-related reactogenicity mirrors symptoms associated with postoperative complications. Operative staff will need to investigate postoperative symptoms thoroughly to correctly identify the likely cause.

Immune time course of COVID-19 vaccine

Summary

- Results from 20 phase I/II/III clinical trials and an additional 80 observational studies were included.
- Trial data suggests immunity following vaccination is generally reached 7 days (Pfizer) or 14 days (AstraZeneca, Janssen, Moderna, Novavax, Sputnik V, Sinovac and Sinopharm) following the final vaccine dose. Real-world data indicates that vaccination confers high levels of protection. However, there is serological evidence suggesting some vaccines may not be as effective against new SARS-CoV-2 variants.
- Poorer immunological responses to COVID-19 vaccines have been reported in patients with haematologic malignancies, patients taking immunomodulators and solid organ transplant recipients. These patients may not be sufficiently immunised towards SARS-CoV-2.
- Elective procedures: existing guidance of separating vaccination and surgical procedures by at least 2 weeks after the final dose would enable sufficient immunity to develop in patients undergoing surgery.
- Emergency procedures: patients who have not received their final dose of COVID-19 vaccines are at risk of acquiring and transmitting SARS-CoV-2. Operating staff must continue to follow COVID safe surgery practices.
- Irrespective of procedure type, vaccinations alone are unlikely to be solely sufficient in mitigating the transmission of SARS-CoV-2. Therefore, there is a continued need for high vigilance (PPE, COVID-safe surgery) when SARS-CoV-2 is circulating in the community, particularly when operating on patients who are vulnerable to reduced vaccine efficacy.

Results

Immune time course of COVID-19 vaccines

A systematic literature search of biomedical and preprint databases and targeted searches of health regulatory agencies websites identified 20 clinical trials that met the PICO criteria. Targeted searches identified an additional 80 observational studies that provided evidence on risk groups, SARS-CoV-2 variants, and real-world efficacy data.

Serology and efficacy results from phase I/II/III trials was used to investigate how long it takes for the immune system to generate a robust response to vaccination against SARS-CoV-2. Most trials measured and reported serological response via anti-spike IgG, T-cell response ($CD4^+$ and $CD8^+$) and neutralising antibodies over time. The Moderna, Novavax, Pfizer and Gamaleya vaccine trials benchmarked the serological response induced by the vaccines to convalescent serum (serum from infected patients). A vaccine was considered to induce a strong immune response if serological markers surpassed those in convalescent serum.[46-48] These measurements provided an indication of vaccine immunogenicity towards SARS-CoV-2. However, there was no standardised approach to assessing vaccine immunogenicity and it was unclear to what extent serological responses correlate

with efficacy. Further, the follow-up duration of clinical trials was limited (1 to 3 months for serological data and 3 to 6 months follow-up for efficacy data). Efficacy was generally inferred by comparing the incidence of symptomatic COVID-19 between the vaccine and control arms in the clinical trials. High efficacy levels were defined as >50% by the WHO.[49]

Clinical trials

A summary of serological markers and efficacy are presented in ***Table 3***. In general, a strong immune response, as inferred by neutralising antibody titres, seroconversion rates or the ability to induce a humoral response, was observed 7 to 14 days after the final vaccine dose.[46,48,50-56] The Janssen vaccine induced high levels of neutralising antibodies 29 days following vaccination.[57] Similarly, high efficacy levels (defined as >50% by the WHO[49]) were observed 7 to 14 days following the final vaccine dose.[58-65]

Collectively, patients have high immunity towards SARS-CoV-2 by 7 days (Pfizer[46,47,50,58]) or 14 days (AstraZeneca,[59] Gamaleya,[56,65] Moderna,[51,52,60] Novavax,[48,62] Janssen, Sinopharm,[53,63] and Sinovac[54,55,64]) after the final vaccine dose.

Table 3 Summary of serological and efficacy data from clinical trials

Vaccine **ID** **Dose schedule**	**Serological response**	**Efficacy (95% CI)**	**Interpretation**
Pfizer[47,48,50] BNT162b2 Days 1 and 22 [a]	Antigen binding IgG and virus neutralising antibody levels boosted after the second dose Antibody response exceeded convalescent serum day 28	Day 1–22: 52.4% (29.5% to 68.4%) Day 22–27: 90.5% (61.0% to 98.9%) Day 28 onwards: 94.8% (89.8% to 97.6%)	High immunity ≥**7 days** following the second dose
AstraZeneca[51,52,59] AZD1222 Days 1 and 4–12 weeks later [b]	NR [c]	≥14 days post-dose 2: 62.1% (41.0% to 75.7%)	Data only available ≥**14 days** following the second dose; therefore efficacy prior to this unknown
Moderna[60] MRNA1273 Days 1 and 29 [a]	Binding and neutralising antibodies increased substantially 14 days after second dose to levels exceeding human convalescent serum	Day 15 onwards: 95.2% (91.2% to 97.4%) Day 42 onwards: 94.1% (89.3% to 96.8%)	High immunity ≥**14 days** following the second dose
Novavax[48,62] NVX-CoV2373 Days 1 and 29 [a]	A strong antibody response exceeding levels in human convalescent serum was observed 14 days after the second dose	Day 1 onwards: 70.4% (58.3% to 79.1%) Day 42 onwards: 89.7% (80.2% to 94.6%)	High immunity ≥**14 days** following the second dose

Vaccine ID Dose schedule	Serological response	Efficacy (95% CI)	Interpretation
Janssen[57,61] Ad26.COV2.S Single dose day 1[d]	High levels of neutralising antibody titres were detected in >90% of people on day 29 following vaccination	Day 15 onwards: 66.9% (59.0% to 73.4%) Day 29 onwards: 66.1% (55.0% to 74.8%)	High immunity ≥**14 days** following the second dose
Sputnik V[56,65] Gam-COVID-Vac Days 1 and 22 [a]	A strong antibody response exceeding levels in human convalescent serum was observed 7 days after the second dose	Any timepoint: 73.1% (63.7% to 80.1%) Day 15 onwards: 87.6% (81.1% to 91.8%) Day 22 onwards: 91.6% (85.6% to 95.2%) Day 29 onwards: 91.1% (83.8% to 95.1%)	High immunity **≥7 days** following the second dose
Sinopharm[53,63] BBIBP-CorV Days 1 and 29 [a]	A humoral response to vaccination was induced in all participants 14 days after the second dose	Any timepoint: WIV04 strain: 50.3% (33.6% to 62.7%) HBO2 strain: 65.5% (52.0% to 75.1%) Day 43 onwards: WIV04 strain: 72.8% (58.1% to 82.4%) HBO2 strain: 78.1% (64.8% to 86.3%)	High immunity ≥**14 days** following the second dose
Sinovac[54,55,64] CoronaVac Days 1 and 15 [a]	High seroconversion rates (92%) of neutralising antibodies were measured 14 days after the second dose	Day 29 onwards: 83.5% (65.4% to 92.1%) [e]	High immunity ≥**14 days** following the second dose

Abbreviations

CI = confidence interval.

Notes

a = Efficacy defined as symptomatic COVID-19 confirmed with lab sample.

b = Efficacy defined as primary symptomatic COVID-19 (fever, cough, shortness of breath, anosmia, ageusia) confirmed with lab sample.

c = Changes in serological markers following the second dose of the vaccine were not reported.

d = Efficacy defined as moderate-severe-critical COVID-19 as defined by a Clinical Severity Adjudication Committee.

e = Efficacy data for days 1–14 and day 15 as presented graphically, lower efficacy was reported at these timepoints.

Real-world evidence

As countries approve and roll out mass vaccination programs to protect against COVID-19, real-world data on the effectiveness of the vaccines is emerging. Emerging data indicates that vaccination confers high efficacy, particularly against hospitalisation and death.[66-69]

Vaccine effectiveness towards SARS-CoV-2 variants

WHO has listed 4 variants of concern: Alpha (B.1.1.7, UK), Beta (B.1.351, B.1.351.1, B.1.351.3, South Africa), Gamma (P.1, P.1.1, P.1.2, Brazil) and Delta (B.1.617.2, AY.1, AY.2, AY.3, India).[70] These variants may have increased transmissibility or virulence compared to wild-type SARS-CoV-2. As these variants become the dominant strain(s), it is important to investigate whether vaccine effectiveness is preserved.

- Alpha variant: the immune response generated by the Pfizer and Janssen vaccines exhibited reduced neutralising activity towards the Alpha variant compared to wild-type SARS-CoV-2.[71-73] However, the Pfizer and AstraZeneca vaccines still maintain high efficacy levels as inferred by the incidence of symptomatic COVID-19: 93.7% (95% CI: 91.6 to 95.3) for the Pfizer vaccine[74] and 70.4% (95% CI: 43.6 to 84.5)[75] to 74.5% (95% CI: 68.4 to 79.4) for the AstraZeneca vaccine.[74]
- Beta variant: the immune response generated by the Pfizer and Janssen vaccines exhibited reduced neutralising activity towards the Beta variant compared to wild-type SARS-CoV-2.[72,73,76-79] The effectiveness of the Pfizer and Novavax vaccines, as inferred by the incidence of symptomatic COVID-19, was reduced (75.0% [95% CI 70.5% to 78.9%] for Pfizer;[80] and 51% [95% CI: -0.6 to 76.2] for Novavax).[81]
- Gamma variant: the immune response generated by the Pfizer vaccine exhibited reduced neutralising activity towards the Gamma variant compared to wild-type SARS-CoV-2.[72]
- Delta variant: the immune response generated by the Moderna vaccine exhibited reduced neutralising activity towards the Delta variant compared to wild-type SARS-CoV-2.[82] However, the Pfizer and AstraZeneca vaccines still maintain high efficacy levels as inferred by the incidence of symptomatic COVID-19: 88.0% (95% CI: 85.3% to 90.1%) for Pfizer and 67.0% (95% CI: 61.3% to 71.8%) for AstraZeneca.[74]

Vaccine response in sub-populations

Inclusion in the clinical trials was generally limited to healthy adults. However, vaccine efficacy may differ in specific sub-populations with altered immune function (e.g. immunosenescence, immaturity or suppression). For example:

- Children and adolescents: The Pfizer,[83] Moderna[84] and Sinovac[85] vaccines induce a comparable serological response in individuals <18 years to that observed in adults. The Pfizer vaccine has a reported efficacy of 100% (95% CI: 75.3% to 100%) in adolescents 12 to 15 years.[83]
- Elderly people: In spite of a lowered serological response after the first Pfizer vaccine dose, older adults exhibit comparable serological response after the second dose to younger adults.[86-89] The efficacy of the mRNA vaccines is also high (>50%) in older adults.[66,90] A similar

serological response to the AstraZeneca vaccine was observed in people aged >70 years and younger cohorts. [91]

- Patients with cancer:
    - Patients with a haematological malignancy have a significantly lowered immunogenicity to mRNA vaccines[92-96] and the AstraZeneca vaccine.[95] This is most pronounced in patients using or with a history of anti-CD-20 antibody treatment,[92,94,96,97] ruxolitinib,[97] Bruton's tyrosine kinase inhibitors[97] or venetoclax.[97]
    - For patients with solid tumours, a lag in immune response following the first vaccine dose with an mRNA vaccine has been observed.[98,99] However, seroconversion occurred for most patients following the second vaccine dose.[99,100] It is unclear whether the efficacy is affected.[98,99]
- Patients with HIV: the AstraZeneca and mRNA vaccines were reported to be immunogenic after 2 doses for patients with well controlled HIV on antiretroviral therapy.[101,102] A single dose of mRNA vaccine produced a variable vaccine response.[102]
- Patients taking immunomodulators:
    - Some patients taking immunomodulators do not produce a detectable immune response following the AstraZeneca, Sinovac or mRNA vaccines.[103] This is most pronounced for patients taking rituximab,[104-106] mycophenolate,[107] abatacept[104,105,108] or glucocorticoids.[105,108]
    - Patients with inflammatory bowel disease had a robust serological response to mRNA or Janssen vaccines.[109]
    - Patients with multiple sclerosis had a variable or reduced serological response to vaccination.[110,111]
- Patients with kidney disease: A systematic review of 35 studies found 70% to 96% of patients undergoing dialysis had a detectable serological response following 2 doses of an mRNA vaccine.[112] Vaccine effectiveness in this population is not known.
- Solid organ transplant recipients: a poor response to vaccination with mRNA and Janssen vaccines was observed in solid organ transplant recipients.[112-127] One study of transplant recipients who developed COVID-19 following full vaccination found 50% required hospitalisation.[113]
- Patients with prior SARS-CoV-2 infection: Patients previously infected with the SARS-CoV-2 virus had an enhanced serological response to a single dose of a mRNA vaccine. In these patients a single dose may be as protective as 2 doses in a virus-naïve population.[128-146]

Vaccination and SARS-CoV-2 transmission

It is not yet known how vaccination impacts SARS-CoV-2 transmission. Data from the United Kingdom suggests that vaccination with either AstraZeneca or Pfizer vaccines may lower household SARS-CoV-2 virus transmission by 40 to 50%.[147]

Recommendations

Immunity following vaccination was generally reached 7 days (Pfizer) or 14 days (AstraZeneca, Gamaleya, Janssen, Moderna, Novavax, Sinovac and Sinopharm) following the final vaccine dose as inferred by serological and efficacy results. Therefore, it is preferable to schedule surgical procedures after this time to allow a high immune response to develop.

Not all patients develop a consistent immune response to vaccination. Patients with haematological malignancy, solid tumours, taking immunomodulators or who received a solid organ transplant had a markedly lowered immune response to COVID-19 vaccines. These patients are at a potentially greater risk of acquiring and transmitting SARS-CoV-2. Additional precautions may be required for the patient and staff throughout the operative period.

Even in the general population, vaccinated individuals can contract and transmit SARS-CoV-2. Likewise, the immunogenicity and efficacy of COVID-19 vaccines may be reduced depending on the circulating SARS-CoV-2 variant(s). Therefore, vaccination alone will likely not be sufficient to ensure total safety from COVID-19. There is a continued need for high vigilance (PPE, COVID-safe surgery) when SARS-CoV-2 is circulating in the community, particularly when operating on patients who are vulnerable to reduced vaccine efficacy.

Elective procedures: Existing guidance of separating vaccination and surgical procedures by at least 2 weeks after the final dose would enable sufficient immunity to develop in patients undergoing surgery. Patients from higher-risk groups may not have sufficient immunity and are at risk of acquiring and transmitting SARS-CoV-2.

Urgent and emergency procedures: Patients who have not received their final dose of COVID-19 vaccines are at risk of acquiring and transmitting SARS-CoV-2. Irrespective of vaccine status, operating staff must continue to follow COVID-safe surgery practices given viral transmission post-vaccination is uncertain.

Immediate reactogenicity following COVID-19 vaccines

Summary

- Results from 9 clinical trials and 6 vaccine safety surveillance databases were included.
- Following vaccination, reactogenicity (local and systemic adverse events) was common, affecting up to 88% of recipients. Reactogenicity was transient (lasting 1 to 3 days), mild, and often occurred more frequently in younger adults (<55–65 years), females, individuals with a history of COVID-19 or a BMI ≥30kg/m^2. Adverse events were more common after the first dose of the AstraZeneca vaccine and after the second dose of the Moderna and Pfizer vaccine.
- For elective procedures, existing guidance of separating COVID-19 vaccination and surgical procedures by at least 1 or 2 weeks would enable reactogenicity symptoms to resolve so that any postoperative symptom can be correctly attributed to the vaccine or the operation.
- For urgent and emergency procedures, reactogenicity symptoms were generally mild and self-limiting. However, their impact on surgical procedures is uncertain. Further, vaccine-related reactogenicity mirrors symptoms associated with postoperative complications. Operative staff will need to investigate postoperative symptoms thoroughly to correctly identify the likely cause.

Results

A systematic literature search of biomedical and preprint databases and targeted searches of health regulatory agencies websites identified 9 clinical trials and 6 vaccine safety surveillance databases that met the PICO criteria.

The clinical trials comprised of eight phase II/III or III trials[10,148-154] and one phase I/II trial.[155] The phase I/II trial for the AstraZeneca vaccine was also included because the phase II/III trial did not report local and systemic adverse events.[156,157] The phase III trial of the Gamaleya Institute vaccine also did not report adverse events[154] and their phase I trial did not include a placebo arm.[158] All trials were multicentre RCTs performed in Africa (k = 2), Asia (k = 1), Europe (k = 4), North America (k = 4) and South America (k = 3). The trials recruited healthy adults (≥16 to 18 years) with no known history of SARS-CoV-2 infection. One trial only enrolled adolescents (12 to 25 years of age).[151] The number of included patients ranged from 1,077 to 44,325, with 5 trials recruiting more than 20,000 patients.[10,148,149,153,154] In most trials, enrolment numbers were based on power calculations for efficacy outcomes, however it was unclear whether the trials were sufficiently powered to detect rare adverse events. Patients were randomised receive to a COVID-19 vaccine or placebo. The vaccines were manufactured by AstraZeneca,[155] Gamaleya,[154] Janssen ,[148] Moderna,[149] NovaVax,[150] Pfizer,[10,151] Sinopharm[153] and Sinovac[152] and were inactive SARS-CoV-2,[152,153] recombinant viral-vectored-[148,150,154,155] protein subunit-,[10,149,151] or mRNA-based vaccines.[10,149,151] The placebo was meningococcal group A, C, W and Y conjugate vaccine,[155] vaccine adjuvant/buffer[10,151,154] or saline.[10,148-151] The Janssen vaccine was single dose, and the remaining vaccines required 2 doses spaced approximately 14 to 28 days apart. Safety outcomes included the occurrence of reactogenicity (local and systemic adverse events) and unsolicited adverse events (includes AESI). Local and systemic adverse events were

monitored for 7 days after each dose and were self-reported via electronic diaries. Adverse events were graded mild, moderate, or severe or scored 1 to 3 (representing mild to severe, respectively). Studies categorised unsolicited adverse events in accordance with existing criteria such as the FDA's toxicity grading criteria or Medical Dictionary for Regulatory Activities. Unsolicited adverse events were monitored for 28 days to 6 months following each vaccine dose and deemed unrelated or likely related to the vaccine. For local and systemic adverse events, the assessed population was often a subset of the entire enrolled population, for unsolicited adverse events, all patients who received one dose were included.

The vaccine safety surveillance databases were informed by passive and active surveillance programs in Australia (AusVaxSafety and Database of Adverse Event Notifications [DAEN]), Aotearoa New Zealand (Centre for Adverse Reactions Monitoring [CARM]/Medsafe), Canada (Health Canada), the UK (Yellowcard, Medicines & Healthcare products Regulatory Agency [MHRA]) and the US (Vaccine Adverse Event Reporting System, Centre for Disease Control and Prevention). The databases reported adverse events for the AstraZeneca, Moderna and Pfizer vaccines. The surveillance databases were accessed on the 31 July 2021 and generally reflected the number of adverse events as of July 2021.

Active surveillance systems captured local and systemic adverse events 3 to 8 days after each vaccine dose.[159-161] The active surveillance systems sent surveys to vaccine recipients asking if they experienced any adverse event following vaccination. In Australia, the survey was distributed to all vaccine recipients. In the US, recipients had to enrol in the surveillance program and in the UK, recipients had to download an app to be included. Adverse events captured by the active surveillance were self-reported and were not clinically verified. It was unclear whether the events were temporal to, or caused by the vaccine. The reported rates may therefore over- or underestimate the true incidence of local and systemic adverse events. The results from the UK app did not report the overall rate; rather, results were delineated by demographic factors.[160]

Passive surveillance systems (Medsafe, DAEN, Health Canada and Yellowcard) captured local, systemic and unsolicited adverse events following vaccination.[162-165] The passive systems relied on the vaccine recipient or healthcare provider self-reporting suspected adverse events to regulatory agencies via forms published on their respective websites. Suspected adverse events were monitored by the agencies and were often clinically investigated if there was an increase in incidence above the background rate. Aside from Guillain-Barre syndrome, myocarditis/pericarditis, and TTS, it was unclear which of the other adverse events were clinically reviewed to establish causality.

Clinical trials

In all vaccine trials, local and systemic adverse events were more common in the vaccine group than the placebo group. Injection site pain was the most common local adverse event reported by 24% to 84% of trial participants (***Table 4***). Redness and swelling occurred less frequently – fewer than 10% of trial participants reported these events. Local adverse events were mild, occurred more often in younger adults (16 to 55–65 years),[10,149] and lasted 2.2 to 2.8 days in one study[150] with a similar incidence after the first and second vaccine dose.

Chills, fatigue, headache, and muscle pain were the most common systemic adverse events and occurred, on average, in 25% to 45% of participants (***Table 4***). The incidence of these events was

generally higher following the second vaccine dose. Diarrhoea, fever, joint pain, and nausea/vomiting were less frequently encountered. It was unclear whether these rarer events occurred more frequently after the first or second dose. Systemic adverse events were mild to moderate with few serious adverse events (<5% of all systemic adverse events). Systemic adverse events lasted 1 to 3 days,[149,150] with few events observed 7 days post-vaccine.[155] Adverse events were more common in younger adults (16 to 55–65 years) compared to older adults (>55–65 years).[10,149] There was no difference in the rate of adverse events between participants aged 12 to 15 and 16 to 25 years.[151]

Surveillance databases

When reported, the number of local and systemic adverse events from passive databases was small and varied considerably, likely due to the difference in total number of vaccinated individuals in Aotearoa New Zealand and Canada. The following discussion will focus on the results from active surveillance databases. For further information regarding the results from all surveillance databases refer to the ***Appendix B***, ***Table 13***.

Injection site pain was the most common local adverse event; it was reported by 47% to 55% of surveyed participants (***Table 4***). Redness and swelling occurred less frequently and were not captured in the AusVaxSafety database. Chills, fatigue, headache, and muscle pain were the most common systemic adverse events and were reported by 9% to 46% of surveyed participants. Diarrhoea, fever, joint pain, and nausea/vomiting were less frequently encountered. The incidence of local and systemic adverse events differed following the first or second vaccine dose. A greater incidence was reported following the first AstraZeneca vaccine dose[166] and the second Moderna and Pfizer dose.[159,160,166] Younger adults (<55-65 years), females, individuals with higher BMI (≤30kg/m^2) and those with prior SARS-CoV-2 infection more were likely to experience an adverse event.[159,160] There was an inconsistent trend among patients with comorbidities, who were more likely to experience an adverse event after the first vaccine dose but less likely after the second dose.[160]

Local and systemic adverse events lasted a mean of 1 day, with fewer than 5% of patients reporting symptoms 7 days post-vaccination.[160]

Table 4 Summary of local and systemic adverse events following COVID-19 vaccines

	Clinical trials [a]		**Active surveillance databases [b]**	
	1st dose Median (min.–max.)	**2nd dose Median (min.–max.)**	**1st dose Median (min.–max.)**	**2nd dose Median (min.–max.)**
Local adverse event				
Pain	62% (24–88%)	61% (65–84%)	47% (20–71%)	55% (15–78%)
Redness	6% (1–15%)	5% (0–7%)	NA (3–7%)	NA (6–19%)
Swelling	7% (1–21%)	6% (0–6%)	7% (5–14%)	NA (10–26%)
Systemic adverse event				
Fatigue	45% (11–70%)	45% (11–66%)	31% (21–42%)	46% (19–60%)
Headache	43% (13–68%)	46% (13–70%)	26% (16–36%)	42% (16–53%)
Muscle pain	25% (5–60%)	39% (6–60%)	19% (11–31%)	35% (12–51%)
Chills	25% (5–56%)	38% (8–80%)	9% (5–26%)	22% (7–40%)
Joint pain	11% (1–43%)	19% (2–30%)	9% (5–20%)	19% (7–32%)

	Clinical trials [a]		Active surveillance databases [b]	
	1st dose Median (min.–max.)	**2nd dose Median (min.–max.)**	**1st dose Median (min.–max.)**	**2nd dose Median (min.–max.)**
Diarrhoea	10% (4–11%)	8% (4–10%)	NA (5%)	NA (6–8%)
Fever	6% (0–87%)	10% (1–70%)	10% (7–18%)	18% (4–38%)
Nausea/vomiting	7% (1–25%)	6% (1–40%)	NA (7–8%)	NA (13–20%)

Notes

a = Vaccine manufacturers contributing to adverse events include AstraZeneca,[155] Janssen,[148] Moderna,[149] Novavax,[150] Pfizer,[10,151] Sinovac,[152] and Sinopharm.[153] Adverse events reported within 7 days of receiving the vaccine.

b = Vaccine manufacturers contributing to adverse events include AstraZeneca,[166] Moderna[159] and Pfizer.[159,166] Adverse events reported within 3 to 7 days after receiving the vaccine. Databases included Australia and US.[159,166]

Recommendations

Following COVID-19 vaccination, local and systemic adverse events (reactogenicity) were common, affecting up to 88% of vaccine recipients. Reactogenicity is the physical manifestation of the body's immune response towards the COVID-19 vaccine[167] and is a commonality across different vaccines.

Injection site pain and generalised cold-like symptoms (e.g. chills, headache, and muscle pain) were commonly encountered reactogenicity symptoms. Reactogenicity was mild and transient, lasting an average of 1 to 3 days, with few events observed 7 days post-vaccination. Reactogenicity disproportionally affected younger adults (<55 to 65 years), females, individuals with BMI ≤30kg/m^2, a history of COVID-19 or were receiving their second Pfizer and Moderna dose or first AstraZeneca dose. It is unclear whether individuals with comorbidities were more burdened by reactogenicity symptoms.

The effect of COVID-19 vaccine reactogenicity on surgical procedures is uncertain. Existing guidelines for childhood vaccination noted 'there is no evidence that recent vaccination increases the risk of complications from either surgery or anaesthesia'.[28] However, reactogenicity presents similarly to symptoms associated with postoperative complications. If patients received the vaccine prior to surgery, it would be difficult to discern regular COVID-19 vaccine reactogenicity to postoperative complications.

Elective procedures: Existing guidelines recommending vaccination and surgery be separated by 1 to 2 weeks would enable the patient to recover from vaccine-related reactogenicity and avoid misattribution of patient's symptoms postoperatively.

Urgent and emergency procedures: Reactogenicity symptoms following COVID-19 were generally mild and self-limiting. However, their impact on surgical procedures is uncertain. Existing guidelines for other vaccines suggest the impact of reactogenicity on operative safety is likely minor and therefore the procedure should likely occur irrespective of vaccine status. Further, vaccine-related reactogenicity mirrors symptoms associated with postoperative complications. Operative staff will need to investigate postoperative symptoms thoroughly to correctly identify the likely cause.

Adverse events of special interest following COVID-19 vaccines

Summary

- Results from 4 surveillance databases, 9 clinical trials and 1 retrospective analysis were included.
- In the general population, AESI were rare to very rare events based on their background incidence. The background incidence of AESI increased with age, particularly for cardiovascular and blood and lymphatic-related events, with events increasingly common among older adults (≥85 years).
- For most AESI, a causal link to COVID-19 vaccines has not been established and it is unclear whether they surpass background rates. AESI casually associated with COVID-19 vaccines are relatively rare events and generally manifest within 2 weeks.
- For elective surgery, existing guidance separating vaccination and surgery by 2 weeks would provide sufficient time for most AESI to manifest. Aside from Guillain-Barre syndrome, myocarditis/pericarditis and TSS, it is unclear whether other AESI are causal to, and occur with greater frequency following COVID-19 vaccines and therefore require unique management strategies beyond what occurs in regular practice. Given the severity of causally associated AESI, if an individual experiences an event, it may warrant a delay to surgery until the patient has recovered.
- For urgent and emergency surgery, given the relative rarity of AESI causally associated with COVID-19 vaccines, it is likely the operation should occur irrespective of vaccine status. Operative staff should familiarise themselves with existing clinical management guidelines for AESI causally related to COVID-19 vaccines to ensure events can be adequately managed if encountered.

Results

The characteristics of the included clinical trials and safety surveillance databases were discussed above.

Background incidence of AESI

The background incidence of AESI was sourced to frame the relative incidence of AESI following COVID-19 vaccines. The background incidence of 15 AESI was informed by Li (2021).[26] The events were sourced from 13 health databases encompassing 8 countries (Australia, France, Germany, Japan, the Netherlands, Spain, UK and the US). The incidence was stratified by age and sex. For this report, the incidence was regrouped to broadly match Australia's current COVID-19 vaccination recommendations (18 to 54 and 55 to ≥85 years). Their analyses included 126,661,070 individuals, of which US residents, females and individuals aged 34 to 55 were the most represented. The Australian databases informed the incidence of deep vein thrombosis, pulmonary embolism, appendicitis, Bell's palsy, anaphylaxis, immune thrombocytopenia and narcolepsy, and the incidence was congruent with the overall trends.

There was significant variability in the background incidence of AESI. However, there were common trends across many AESI (***Table 5***). For immune- and nervous system disorders, the incidence increased with age, transitioning from very rare (<1/100,000) to rare (<1/1,000 to ≥1/10,000) events in the older age groups. The incidence of these events was generally similar between males and females.

For cardiovascular and blood and lymphatic disorders, particularly deep vein thrombosis, myocardial infarction, stroke and pulmonary embolism, the incidence increased with age, transitioning from very rare (<1/100,000) and rare (<1/1,000 to ≥1/10,000) to uncommon (<1/100 to ≥1/1,000) or common events (<1/10 to ≥1/100) in the older age group (55 to **≥**85 years). The incidence of stroke, myocardial infarction and myocarditis/pericarditis was higher in males than females. The incidence of appendicitis decreased with age, transitioning from an uncommon (<1/100 to ≥1/1,000) to rare event (<1/1,000 to ≥1/10,000) with approximately equal incidence between sexes.

Table 5 Summary of the background incidence of AESI

AESI category	**Annualised incidence per 100,000 persons Age: 18 to 54 years**	**Annualised incidence per 100,000 persons Age: 55 to ≥85 years**
Immune system Guillain-Barre syndrome, immune thrombocytopenia, disseminated intravascular coagulation, anaphylaxis	Very rare to rare 3 to 39 events per 100,000 persons per year	Very rare to rare 5 to 56 events per 100,000 persons per year
Cardiovascular system Acute myocardial infarction, myocarditis/pericarditis	Very rare to uncommon 6 to 172 events per 100,000 persons per year	Uncommon to common 171 to 1,514 events per 100,000 persons per year
Blood and lymphatic system Haemorrhagic and non-haemorrhagic stroke, deep vein thrombosis, pulmonary embolism	Rare to uncommon 18 to 119 events per 100,000 persons per year	Uncommon to common 125 to 1,523 events per 100,000 persons per year
Nervous system Bell's palsy, Encephalomyelitis, transverse myelitis, narcolepsy	Very rare 2 to 68 events per 100,000 persons per year	Very rare to rare 2 to 100 events per 100,000 persons per year
Infections Appendicitis	Rare to uncommon 85 to 146 events per 100,000 persons per year	Rare 35 to 66 events per 100,000 persons per year

Notes

The lowest and highest mean number of events per body system was reported for each age group.
The relative incidence was classified as very common (≥1/10,), common (<1/10 to ≥1/100), uncommon (<1/100 to ≥1/1,000), rare (<1/1,000 to ≥1/10,000) and very rare events (<1/100,000).

AESI incidence from clinical trials

Nine phase II/III clinical trials provided evidence on AESI following COVID-19 vaccines.[155] Overall, treatment-related AESI were infrequently encountered, with trials reporting 0 or 1 events per treatment group (see ***Appendix B, Table 15***). Three trials reported no treatment-related AESI.[148] When reported, AESI occurred 3, 6 and 14 days after the second vaccine dose (myocarditis,[149] deep vein thrombosis,[150] and transverse myelitis,[10,151] respectively). There were no reported cases of thrombocytopenia syndrome or myocarditis/pericarditis in the AstraZeneca[156,157] and Pfizer trials,[10,151] respectively. The incidence of AESI per 100,000 persons was not calculated because the trials were underpowered to detect rare events, which may lead to the results over- or under-estimated the true incidence.

Given there remains uncertainty regarding which AESI are causal to the vaccines, all serious adverse events reported in the clinical trials were also reported (noting they were not listed as treatment-related) (see ***Appendix B, Table 16***). Numeric imbalances were observed in the Janssen trial, with higher incidence of thromboembolic events (pulmonary embolism and deep vein thrombosis) and seizures observed in the vaccine group compared to the placebo group (11 vs 3, and 4 vs 1 events, respectively).[148] The authors noted the patients had predisposing factors that may have contributed to the events, and a causal relationship between the vaccine and the event was not found for 12 of the 14 thromboembolic events.

AESI incidence from surveillance databases

Four databases from Aotearoa New Zealand,[164] Australia,[161,162] Canada,[165] and the UK[160] provided evidence on AESI following COVID-19 vaccination. The results reflect the number of AESI as of July 2021. Because it was unclear which of these events were clinically reviewed, their causality in relation to the COVID-19 vaccines remained uncertain, and therefore only a high-level summary of events is provided (***Table 6***). Owing to the uncertainty, these results should be interpreted cautiously. AESI that are causally related to COVID-19 vaccines are discussed further below.

All AESI

Overall, the relative incidence of AESI varied significantly by body system, database, and manufacturer (***Table 6*** and ***Appendix B, Table 17*** and ***Table 18***). AESI were relatively rare events, with most reporting an incidence less than 1 per 100,000 doses administered. Herpes, stroke, Bell's palsy, anaphylaxis, and TTS had the highest adverse event rate across all databases (1 to 3 events per 100,000 doses in at least 2 databases).

Case series and reports were searched to identify when AESI occurred following the COVID-19 vaccines owing to the lack of evidence provided in databases and clinical trials. Most of the AESI were not clinically verified as causally associated with COVID-19 vaccines, which may have contributed to the variable presentation time (from minutes to months post-vaccination). Generally, AESI occurred within 2 weeks following the vaccination (***Table 6*** and ***Appendix B, Table 19***). The incidence of events tended to occur after the first dose. However, this remains uncertain given the quality of evidence.

Table 6 Summary of the incidence and onset of AESI following COVID-19 vaccines

AESI category	Incidence per 100,000 doses (cumulative)	Separation between vaccination and presentation of AESI
Immune system Guillain-Barre syndrome, immune thrombocytopenia, disseminated intravascular coagulation, anaphylaxis	0.11–3.3 per 100,000 doses	Range, 1–51 days Most AESI presented within 14 days Anaphylaxis, 2–180 minutes
Cardiovascular system Myocardial infarction, heart failure, myocarditis/pericarditis	0.0014–1.65 per 100,000 doses	Myocarditis/pericarditis, 1–94 days, most within 14 days Myocardial infarction and heart failure, 0.5–6 hours
Blood and lymphatic system Embolism, deep vein thrombosis, vasculitis, haemorrhage, disseminated intravascular coagulation, microangiopathy	0.05–2.17 per 100,000 doses	Range, 2–28 days Most AESI presented within 14 days
Respiratory system Acute respiratory distress syndrome	0.002–0.006 per 100,000 doses	14 days
Hepato-gastrointestinal and renal system Acute kidney injury, acute liver injury, acute pancreatitis, appendicitis	0.0–0.49 per 100,000 doses	Range, 10–13 days All AESI presented within 14 days
Nervous system Aseptic meningitis, encephalitis, acute disseminated encephalomyelitis, stroke, Bell's palsy/facial paralysis, myelitis, generalised convulsion, subacute thyroiditis	0.0–2.03 per 100,000 doses	Range, 1–48 days Most AESI presented within 14 days
Infections and musculoskeletal Erythema multiforme, arthritis, herpes zoster, chilblain-like lesions, rhabdomyolysis	0.01–3.17 per 100,000 doses	Range, 1–12 days Most AESI presented within 7 days

Notes

The minimum and maximum number of events were reported. Results reflect reporting as of July 2021.

Source

Information was sourced from vaccine safety surveillance databases in New Zealand,[164] Australia,[161] Canada,[165] and the UK.[163]

Causal or suspected causal AESI

TTS was a relatively rare event and predominantly associated with the AstraZeneca vaccine. The incidence was greater among younger adults (less than 50–60 years), ranging from 2.05[163] to 3.30[161] per 100,000 doses. Among older adults (greater than 50–60 years), the incidence was 1.08[163] to 1.70[161] per 100,000 doses, respectively. The incidence was less following the second AstraZeneca dose in younger adults and other COVID-19 vaccines (e.g. 0.03 to 0.05 per 100,000 doses for Pfizer; it was

unclear whether these events were clinically verified).[163] It was unclear whether the events occurred more frequently in males or females with databases reporting opposing results.[161,163,165] In Australia, severe cases of TTS were more common in females; most patients were older than 50; and the median onset of symptoms/diagnosis was 12 days, ranging from 1 to 51 days.[161] A similar age (median 56 years) and time to onset was observed in Canada (1 to 34 days).[165] Clinical guidance on the management of TTS has been published by the Department of Health[168] and the British Society for Haematology.[169]

Myocarditis and pericarditis were relatively rare events, and were predominately associated with mRNA vaccines.[165] The incidence of myocarditis or pericarditis following Moderna vaccine ranged from 1.20[165] to 1.47[163] per 100,000 doses and from 0.43[163] to 0.59[165] per 100,000 doses following the Pfizer vaccine. In Aotearoa New Zealand, Australia and the UK, the events presented within 14 days and occurred more frequently after the second Pfizer dose and in younger males.[161,163,170] In Canada, myocarditis and pericarditis occurred more frequently in younger males within 4 hours to 94 days after vaccination. More events occurred after the second Moderna dose and first Pfizer dose.[165] Clinical guidance on the management of myocarditis and pericarditis has been published by the Department of Health.[171]

Guillain-Barre syndrome was a relatively rare event, ranging from 0.06 to 0.91 per 100,000 doses. In Australia, Canada and the UK, Guillain-Barre syndrome was more commonly reported following the AstraZeneca vaccine.[161,163,165] In Canada, the events presented 3 to 25 days following vaccination; generally occurred after the first vaccine dose; were more likely to be reported among older males (median age 56 years) and was above the expected background rate.[165] No demographic information was provided by Australian and UK databases. Clinical guidance on the management of Guillain-Barre syndrome in relation to the COVID-19 vaccine has not been published.

Table 7 Summary of AESI causal or suspect causal to COVID-19 vaccines

AESI	Incidence	Onset	Severity/ resolution	Risk factors	Guidance
Guillain-Barre syndrome	0.06–0.91 per 100,000	*Canada* 3–25 days	No information	Increased incidence AstraZeneca vaccine	None
Myocarditis and pericarditis	*Pfizer* 0.43–0.59 per 100,000 doses *Moderna* 1.20–1.47 per 100,000 doses	*Aotearoa New Zealand/ Australia* Usually within 14 days *Canada* 1 hour–94 days	*UK* Events are mild, transient, recover in a short time *Aotearoa New Zealand* Not all patients required hospitalisation	Increased incidence mRNA vaccines Second dose Younger adults	Department of Health[171]

AESI	Incidence	Onset	Severity/ resolution	Risk factors	Guidance
Thrombosis with thrombo-cytopenia	*Younger adults* 2.05–2.60 per 100,000 doses *Older adults* 1.08–1.70 per 100,000 doses	*Australia* Median 12 days (1–51 days) *Canada* 1–34 days	*Australia* 87 cases, 5 deaths, 26 cases required ICU, 57 discharged *Canada* 67 cases, 6 deaths	Increased incidence: AstraZeneca vaccine First dose Younger adults (<50–60 years)	Department of Health[168] The British Society for Haematology.[169]

Notes

The information provided reflects the number of events reported as of July 2021.

Source

Information was sourced from vaccine safety surveillance databases in New Zealand,[164] Australia,[161] Canada,[165] and the UK.[163]

Recommendations

The incidence of AESI following COVID-19 vaccination is uncertain however, the events appeared to be relatively rare. Three AESI were considered causal or were suspected to be causal to COVID-19 vaccines: Guillain-Barre syndrome, myocarditis/pericarditis, and TTS. TTS and Guillain-Barre syndrome are associated with the AstraZeneca vaccine whereas myocarditis and pericarditis are associated with mRNA vaccines. For TTS and myocarditis/pericarditis, younger adults were at greater risk of experiencing the AESI. It is uncertain whether other patient demographics are associated with an increased risk of experiencing an AESI. Guillain-Barre syndrome, myocarditis/pericarditis and TTS were relatively rare events and typically occurred within 2 weeks post-vaccination. These events can be severe and potentially complicate surgical care given their involvement in cardiovascular function and clotting. Therefore:

Elective procedures: AESI following COVID-19 vaccination are relatively rare events. However, they have the potential to adversely affect surgical care owing to their involvement in cardiovascular function and clotting. Existing guidelines of separating vaccination and surgery by 2 weeks would likely provide sufficient time for TTS and myocarditis/pericarditis to manifest. Given the severity of causally associated AESI, if an individual experiences an event, it may warrant a delay to surgery until the patient has recovered. Operative staff should familiarise themselves with existing management guidelines for these AESI. It is unclear whether other AESI are causal to and occur with greater frequency following COVID-19 vaccines (noting the background rates of events are rare to very rare) and therefore require unique management strategies beyond what occurs in regular practice.

Urgent and emergency procedures: Given the relative rarity of AESI causally associated with COVID-19 vaccination, it is likely surgery should occur irrespective of vaccine status. Operative staff should familiarise themselves with existing management guidelines for these AESI to ensure events can be adequately managed if encountered.

Discussion

The overarching aim of this review was to discern the influence of the COVID-19 vaccine on surgical planning and care. To address the aims, a systematic and targeted search of biomedical databases and grey literature was performed. The results of the review were informed by clinical trials, case series, guidelines, vaccine surveillance safety databases and input from a working group of anaesthetists, immunologists, surgeons, and virologists.

The review recommends separating COVID-19 vaccination and elective surgery by 2 weeks after the final dose. The recommendation was based on existing guidance, the resolution of vaccine-related reactogenicity, the typical presentation time of AESI, and time for the patient to become immunised towards SARS-CoV-2. The delay would avoid misattributing vaccine reactogenicity as postoperative complications and minimise the risk of acquiring and transmitting SARS-CoV-2 to the operating staff and other patients. These recommendations apply to major and minor surgery as there was insufficient evidence to delineate between the two. However, the working group additionally noted after major surgery clinicians need to consider whether patients have returned to normal activity levels or their conditioned stabilised before vaccinating. The findings reinforce RACS's earlier position specifying patients should be vaccinated against SARS-CoV-2 prior to surgery.[17] Unvaccinated operative staff and patients are at risk of acquiring and transmitting SARS-CoV-2 in the hospital, and perioperative COVID-19 increases postoperative complications and mortality, with the greatest effect observed for older adults and patients with cancer, or patients undergoing emergency or major surgery.[13-15] Vaccination reduces COVID-19-related postoperative mortality and morbidity, particularly in higher-risk populations[16] and suggests these patients should be prioritised during the vaccine rollout. Vaccination may also help reduce the transmission of SARS-CoV-2 between operating staff and patients who are in close proximity for extended periods of time. If patients undergoing surgery have a choice in COVID-19 vaccines, those that confer the shortest time to complete immunity and have the greater safety profile should be utilised.[35] COVID-safe surgery should still be followed to minimise spread even if the patient and operative staff are vaccinated.

It is recommended urgent and emergency surgery should likely occur irrespective of vaccine status. The recommendation is based on existing guidance, the relative rarity of AESI, the mildness of reactogenicity symptoms and the implementation of existing COVID-19 free surgery policies that minimise SARS-CoV-2 transmission. However, the operating staff and patient need to be aware of the inherent risk of proceeding with the operation. Specifically, they are at risk of acquiring and transmitting SARS-CoV-2, potentially increasing the likelihood of COVID-19-related postoperative complications and mortality;[13-15] AESI may occur, complicating the procedure and postoperative care; and vaccine-related reactogenicity mirrors symptoms associated with postoperative complications. To minimise the potential impact of COVID-19 on surgical care, operating staff should be vaccinated, practise appropriate methods to minimise transmission, be informed of the risk associated with AESI, and know how to manage AESI. Clinical guidance on the management of myocarditis/pericarditis and TSS is available.[168,169,171] Lastly, practitioners are encouraged to ask about the patient's COVID-19 and vaccine status prior to the operation. In the absence of this knowledge, or if patients have received one or both doses, operating staff should implement appropriate policies to minimise viral transmission.[172-175]

The recommendations listed in the review focus on when to vaccinate prior to surgery. It was difficult to create recommendations on when to vaccinate post-surgery given the limited evidence base addressing this period, the breadth of surgical practice and duration of recovery. From an immunological perspective, surgery dysregulates the immune system – an effect lasting days to weeks post-surgery.[176-178] The extent of immune dysregulation is proportional to the magnitude of insult (e.g. major vs minor surgery) and the type and frequency of perioperative medication. The dysregulation reflects alterations to both cell mediated and humoral arms of the adaptive immune system.[176] These processes are paramount when generating an appropriate immune response towards vaccines[179] and if compromised potentially impact the efficacy of the vaccine.[180] Note that the efficacy of COVID-19 vaccines are yet to be explored in post-surgical patients. Further, certain blood products used during surgery (e.g. packed red blood cells, whole blood) and intravenous immunoglobulin are contraindications to MMRV vaccination and require prolonged intervals (0–11 months) between receiving the product and the MMRV vaccine.[44] It is unclear whether the delays following blood products are additionally required following COVID-19 vaccines given the vaccine platforms differ to MMRV vaccines. While existing guidelines recommend delaying the vaccination at least 1 or 2 weeks post-surgery (***Table 2***), it was unclear whether these were evidence based, and allowed sufficient time for the patient and their immune system to recover. Given this uncertainty, the decision on when vaccinate post-surgery should be pragmatic and likely once the patient has returned to normal activity levels, or when their condition has stabilised.

The recommendations listed in the report are primarily applicable to healthy adults. There was limited evidence evaluating the safety and efficacy of COVID-19 vaccines in higher-risk groups. However, patients with a history of cancer, patients using immunomodulators, or recipients of solid organ transplants displayed blunted immune responses towards COVID-19 vaccines and may be more susceptible to acquiring and transmitting SARS-CoV-2 during surgery. Again, COVID-safe surgery policies should still be followed to minimise viral transmission when operating on patients, particularly if patients do not exhibit a strong immunological response to COVID-19 vaccines. Higher-risk patients may also require different delays between surgery and postoperative vaccination, as existing guidelines recommended 1 to 3 months delay for patients who recently underwent transplant surgery.[32] They may also require an additional third vaccine dose to ensure sufficient immunogenicity.[181] The delay likely relates to the use of immunosuppressive medication which blunts the immune response to COVID-19 vaccines. If possible, patients who will require immunosuppressive medication postoperatively should be vaccinated prior to surgery to ensure they generate a robust immune response towards SARS-CoV-2. In addition, clinicians should be aware younger adults and females are disproportionally burdened by vaccine-related reactogenicity and AESI. The increased incidence and severity of reactogenicity potentially relates to the degree of immune activation following the vaccine,[182] with younger adults exhibiting more robust immune response towards vaccines, which may underscore the greater symptoms experienced.[183] However, it remains unclear why younger adults are at greater risk of experiencing AESI, and further research is required.

The limitations of the review relate mainly to the identification and incidence of AESI. The estimates and applicability of AESI sourced from safety surveillance databases and case series was uncertain because:

- It was unclear which AESI were clinically verified, met the Brighton Collaborations case definitions, and were causal to COVID-19 vaccines.
- The population captured in the Australian and Aotearoa New Zealand surveillance databases differ to those providing background estimates (primary healthcare workers, higher-risk patients, and older adults vs general population) and to other international surveillance databases (where the vaccine rollout has been expanded to all adults).
- The number of events per patient and the delineation between events per first or second vaccine dose could not be ascertained given databases generally reported total administered doses.

Collectively, these uncertainties lower the generalisability of the results and limit the ability to compare the incidence post COVID-19 vaccination to background rates and compare the incidence between difference COVID-19 vaccines. The incidence of AESI following COVID-19 vaccines will become more certain as time progresses and the rollouts expand to the broader population. Active pharmacovigilance and safety monitoring will remain paramount in capturing these events. Other limitations of the review relate to the use of a single author to select and review articles, and the targeted approach for sourcing information. This approach was pragmatically necessary but may bias the results of the review.

Conclusion

Separating COVID-19 vaccination and elective surgery by 2 weeks is likely appropriate based on existing guidelines, time to generate immunity, resolution of reactogenicity, and the presentation of AESI following vaccination. After major procedures, patients should also have returned to normal activity levels or their conditioned stabilised before vaccinating. Emergency and urgent surgery should occur irrespective of vaccine status. However, operating staff need to be aware of the risk recent COVID-19 vaccines poses to surgery (confounding postoperative complications, AESI may complicate surgical care, and staff and patients are at risk of viral transmission if immunity has not yet developed). Irrespective of vaccine status, operating staff should utilise COVID-19-free surgical pathways and implement appropriate policies to minimise viral transmission. The results reinforce the position that all patients be vaccinated in a timely manner prior to surgery.

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Appendix A Search strategy

Table 8 Search strategy for MEDLINE via OVID (28 May 2021)

Number	Search terms	Results
1	'BNT162b2'.mp.	245
2	'mRNA-1273'.mp.	137
3	'AZD1222'.mp.	40
4	'ChAdOx1*'.mp.	151
5	'Ad26?COV2?S'.mp.	26
6	'JNJ-78436735'.mp.	0
7	'Convidecia'.mp.	0
8	Gam-COVID-Vac.mp.	4
9	'rAd26-S+rAd5-S'.mp.	0
10	'CoronaVac'.mp.	10
11	'Sputnik V'.mp.	22
12	'BBIBP-CorV'.mp.	5
13	'Covaxin'.mp.	9
14	'BBV152'.mp.	9
15	'NVX-CoV2373'.mp.	14
16	Vaccines/	22,657
17	vaccine*.mp.	332,644
18	vaccination*.mp.	182,278
19	Immuni?ation*.mp.	167,692
20	immuni?e.mp.	4,553
21	Immunization/	5,1627
22	*Coronavirus Infections/	41,768
23	(COVID-19 or COVID19).mp.	132,717
24	((pneumonia or COVID* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*) and (hubei or wuhan or beijing or shanghai)).ti,kf.	1389
25	Wuhan virus*.ti,kf.	10
26	(19nCoV or 2019-nCoV or 2019nCoV).ti,kf.	976
27	(nCoV* or n-CoV*).ti,kf.	1,127
28	("CoV 2" or CoV2).ti,kf.	33,370
29	(OC43 or NL63 or 229E or HKU1 or HCoV* or Sars-coronavirus*).ti,kf.	1,521
30	(2019-novel CoV or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or ((novel or new or nouveau) adj2 (CoV or nCoV or COVID or coronavirus* or corona virus or Pandemi*2)) or (coronavirus* and pneumonia)).ti,kf.	4,977
31	COVID-19.rx,px,ox.	4,056
32	severe acute respiratory syndrome coronavirus 2.mp.	14,035
33	severe acute respiratory syndrome coronavirus 2.ti,kf.	2,876
34	(SARSCoV* or SARS-CoV* or SARS2 or SARS-2).ti,kf.	34,247

Number	Search terms	Results
35	(novel coronavirus* or novel corona virus* or novel CoV).ti,kf.	2,969
36	((coronavirus* or corona virus*) adj2 "2019").ti,kf.	9,475
37	((coronavirus* or corona virus*) adj2 "19").ti,kf.	1,668
38	(coronavirus 2 or corona virus 2).ti,kf.	3,137
39	COVID*.ti,kf.	111,137
40	COVID-19 Vaccines/	2,699
41	COVID-19 Vaccines/ae	233
42	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15	514
43	16 OR 17 OR 18 OR 19 OR 20 OR 21	462,757
44	22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39	143,822
45	44 AND (42 OR 43 OR 41 OR 41)	2,699
46	45 AND adverse event filter	2,993
47	45 AND pharmacovigilance terms	2,863

Table 9 Regulatory agencies and medical societies searched for clinical guidelines

Regulatory agency or medical society	Website	Date searched
Australia and Aotearoa New Zealand		
Royal Australasian College of Surgeons	https://www.surgeons.org/	8/06/2021
Australian Orthopaedic Association	https://www.aoa.org.au/	8/06/2021
Australasian Society of Aesthetic Plastic Surgeons	https://aestheticplasticsurgeons.org.au/	8/06/2021
Neurosurgical Society of Australasia	https://www.nsa.org.au/	1/06/2021
Australasian Society of Clinical Immunology and Allergy	https://www.allergy.org.au/	8/06/2021
Australian and New Zealand College of Anaesthetics and Faculty of Pain Medicine	https://www.anzca.edu.au/	10/06/2021
New Zealand Association of General Surgeons	https://www.nzags.co.nz/	16/01/2021
Australian and New Zealand Society of Cardiac and Thoracic Surgeons	https://anzscts.org/	17/06/2021
Australian Society of Plastic Surgeons	https://plasticsurgery.org.au/	18/06/2021
Medical Oncology Group of Australia	https://www.moga.org.au/	18/06/2021
Cardiac Society of Australia and New Zealand	https://www.csanz.edu.au/	21/06/2021
Australian and New Zealand Association of Paediatric Surgeons Inc.	https://www.anzaps.org/	22/06/2021
The New Zealand Society of Otolaryngology Head and Neck Surgery Inc.	https://www.orl.org.nz/	22/06/2021
The Australian Society of Otolaryngology Head and Neck Surgery	http://www.asohns.org.au/	22/06/2021
General Surgeons Australia	https://www.generalsurgeons.com.au/	22/06/2021
Australian and New Zealand Society for Vascular Surgery	https://www.anzsvs.org.au/	22/06/2021
Colorectal Surgical Society of Australia and New Zealand	https://www.cssanz.org/	22/06/2021
Australian and New Zealand Endocrine Surgeons	https://www.endocrinesurgeons.org.au/	22/06/2021
Urological Society of Australia and New Zealand	https://www.usanz.org.au/	22/06/2021
The Thoracic Society of Australia and New Zealand	https://www.thoracic.org.au/	22/06/2021

Regulatory agency or medical society	Website	Date searched
Australian and New Zealand Metabolic and Obesity Surgery Society	https://anzmoss.com.au/	23/06/2021
Department of Health	https://www.health.gov.au/	7/01/2021
The Australian Council on Healthcare Standards	https://www.achs.org.au/	18/06/2021
Joanna Briggs Institute	https://jbi.global/#	23/06/2021
Best Practice Advocacy Centre, New Zealand	https://bpac.org.nz/	23/06/2021
Canada		
Royal College of Physicians and Surgeons of Canada	https://www.royalcollege.ca/rcsite/home-e	8/06/2021
Canadian Anesthesiologists' Society	https://www.cas.ca/en/home#	11/06/2021
Canadian Society of Otolaryngology–Head and Neck Surgery	https://www.entcanada.org/	11/06/2021
College of Physicians and Surgeons of Alberta	https://cpsa.ca/	21/06/2021
College of Surgeons and Physicians of British Columbia	https://www.cpsbc.ca/	21/06/2021
College of Physicians and Surgeons of Ontario	https://www.cpso.on.ca/	21/06/2021
Canadian Society for Aesthetic Plastic Surgery	https://csaps.ca/	21/06/2021
The Canadian Agency for Drugs and Technologies in Health	http://www.cadth.ca/	03/06/2021 04/07/2021
Alberta Medical Association	https://www.albertadoctors.org/	24/06/2021
Europe		
The European Association of Neurosurgical Societies	https://www.eans.org/	10/06/2021
The World Society of Emergency Surgery	https://www.wses.org.uk/	10/06/2021
European Society for Vascular Surgery	https://www.esvs.org/	10/06/2021
Austrian Federal Office for Safety in Health Care	https://www.basg.gv.at/en/	16/06/2021
European Academy of Neurology	https://www.ean.org/	16/01/2021
European Society of Anaesthesiology and Intensive Care	https://erassociety.org/european-society-of-anaesthesiology-and-intensive-care-esaic/	17/06/2021
European Centre for Disease Prevention and Control	https://www.ecdc.europa.eu/en	15/06/2021
European Medicines Agency	https://www.ema.europa.eu/en	15/06/2021
Norwegian Medicines Agency	https://legemiddelverket.no/English	16/06/2021
Federal Agency for Medicines and Health Products, Belgium	https://www.famhp.be/en	16/06/2021
Global		

Regulatory agency or medical society	Website	Date searched
World Federation of Neurosurgical Societies	https://www.wfns.org/all-member-societies	15/06/2021
World Federation of Societies of Anaesthesiologists	https://wfsahq.org/	15/06/2021
World Federation of Neurology	https://wfneurology.org/	15/06/2021
World Health Organization	https://www.who.int/	15/06/2021
Health Products Regulatory Authority, Ireland	https://www.hpra.ie/	16/06/2021
United Kingdom		
Association of Paediatric Anaesthetists of Great Britain and Ireland	https://www.apagbi.org.uk/	10/06/2021
Royal College of Surgeons of England	https://www.rcseng.ac.uk/	02/06/2021 04/06/2021 7/06/2021
Royal College of Surgeons in Ireland	https://www.rcsi.com/	10/06/2021
Royal College of Physicians of Ireland	https://www.rcpi.ie/#	16/06/2021
British Society for Rheumatology	https://www.rheumatology.org.uk/	11/06/2021
British Orthopaedic Association	https://www.boa.ac.uk/	11/06/2021
British Association of Paediatric Surgeons	https://www.baps.org.uk/	11/06/2021
The Vascular Society of Great Britain and Ireland	https://www.vascularsociety.org.uk/default.aspx	15/06/2021
British Association of Plastic Reconstructive and Aesthetic Surgeons	https://www.bapras.org.uk/	15/06/2021
Association of Surgeons of Great Britain and Ireland	https://www.asgbi.org.uk/	15/06/2021
The Society of British Neurological Surgeons	https://www.sbns.org.uk/	15/06/2021
The British Association of Urological Surgeons	https://www.baus.org.uk/	15/06/2021
British Association of Oral and Maxillofacial Surgeons	https://www.baoms.org.uk/#MainForm	15/006/2021
Society for Cardiothoracic Surgery in Great Britain and Ireland	https://scts.org/	15/06/2021
Neuro Anaesthesia & Critical Care Society	https://naccs.org.uk/	10/06/2021
Royal College of Anaesthetists	https://www.rcoa.ac.uk/	10/06/2021
National Cancer Control Programme, Ireland	https://www.hse.ie/eng/services/list/5/cancer/	10/06/2021
National Institute for Health and Care Excellence	http://www.nice.org.uk/	8/06/2021

Regulatory agency or medical society	Website	Date searched
The Federation of Surgical Specialty Associations	https://fssa.org.uk/default.aspx	8/06/2021
Scottish Intercollegiate Guidelines Network	https://www.sign.ac.uk/	3/06/2021 7/06/2021
The Regulation and Quality Improvement Authority	https://www.rqia.org.uk/	24/06/2021
UK Department of Health and Social Care	https://www.gov.uk/government/organisations/department-of-health-and-social-care	24/06/2021
United States of America		
Agency for Healthcare Research and Quality	https://www.ahrq.gov/research/findings/index.html	01/06/2021 3/06/2021 4/06/2021
American College of Surgeons	https://www.facs.org/	02/06/2021 04/06/2021
American Academy of Orthopaedic Surgeons	https://www.aaos.org/	02/06/2021 03/06/2021
American Academy of Cosmetic Surgery	https://www.cosmeticsurgery.org/	17/06/2021
American Association of Anesthesiologists	https://www.asahq.org/	4/06/2021 07/06/2021
American College of Physicians	https://www.acponline.org/?_ga=2.201714391.794423980.1623122735-1719026746.1623122735	8/06/2021
American Journal of Kidney Diseases	https://www.ajkd.org/	08/06/2021
American Academy of Facial Plastic and Reconstructive Surgery, Inc.	https://www.aafprs.org/	17/06/2021
American Academy of Neurology	https://www.aan.com/	17/06/2021
American Academy of Otolaryngology–Head and Neck Surgery	https://www.entnet.org/	17/06/2021
American Association for Hand Surgery	https://handsurgery.org/	17/06/2021
American Association for Thoracic Surgery	https://www.aats.org/aatsimis/AATSWeb	17/06/2021
American Association of Neurological Surgeons	https://www.aans.org/	17/06/2021
American Society of Plastic Surgeons	https://www.plasticsurgery.org/	17/06/2021
American Orthopaedic Association	https://www.aoassn.org/	17/06/2021
American Orthopaedic Foot & Ankle Society	https://www.aofas.org/	17/06/2021
The American Society of Breast Surgeons	https://www.breastsurgeons.org/	17/06/2021
American Society of General Surgeons	https://theasgs.org/	17/06/2021

Regulatory agency or medical society	Website	Date searched
American Society of Transplant Surgeons	https://asts.org/	17/06/2021
Congress of Neurological Surgeons	https://www.cns.org/Default.aspx	17/06/2021
Centers for Disease Control and Prevention	https://www.cdc.gov/	01/06/2021 02/06/2021
Food and Drug Administration	https://www.fda.gov/	02/06/2021
Society for Vascular Surgery	https://vascular.org/	17/06/2021

Appendix B Results

Table 10 Study characteristics from key vaccine clinical trials

Author (year) location	Setting Study design Follow-up	Eligibility criteria	Patient demographics	Vaccine information [a]
Pfizer trials				
Walsh (2020)[20] USA	Phase I trial RCT 28 days	Healthy adults 18–55 or 65–85 years. Excluded were patients: with known HIV, HCV, or HBV; immunocompromised; history of autoimmune disease; previous diagnosis of COVID-19; receipt of medications intended to prevent COVID-19; prior coronavirus vaccination; a positive test for SARS-CoV-2 antibodies.	Cohort 1 18-55 years Age: 36.7 years (SD 10.95) Male: 42.2% Cohort 2 65-85 years Age: 69.3 years (SD 4.09) Male: 37.8%	Type: mRNA Dose: 30 µg Schedule: Two doses 21 day apart
Sahin (2021)[21] Germany	Phase I/II trial Non-randomised comparative 85 days	Healthy men and non-pregnant women 18–85 years.	Male: 43.8% Age: 39.9 years (SD 10.26)	Type: mRNA Dose: 30 µg Schedule: Two doses 21 day apart
Polack (2020)[21] USA, Argentina, Brazil, South Africa, German, Turkey	Phase III trial RCT 2 months (median)	Adults > 16 years, healthy or had stable chronic medical conditions, including HIV, hepatitis B virus, or hepatitis C virus infection, Exclusion criteria: medical history of Covid-19, treatment with immunosuppressive therapy, or diagnosis with an immunocompromising condition.	Age: median 52 years (range 16–91) Male: 50.6%	Type: mRNA Dose: 30 µg Schedule: Two doses 21 day apart
Frenck (2021)[22] USA	Phase III trial RCT 28 days	Healthy or had stable pre-existing disease, 12–25 years without prior SARS-CoV-2 infection.	Vaccine 12-15 years Age: 13.6 (SD 1.11) Male: 50.1% Vaccine 16-25 years	Type: mRNA Dose: 30 µg Schedule: Two doses 21 day apart

Author (year) location	Setting Study design Follow-up	Eligibility criteria	Patient demographics	Vaccine information [a]
			Age: 19.4 (SD 3.26) Male: 47.5% Placebo12-15 years Age: 13.6 (SD 1.11) Male: 51.8% Placebo 16-25 years Age: 19.6 (SD 3.33) Male: 48%	
AstraZeneca trials				
Vosey (2021)[23] UK and Brazil	Phase III trial RCT 3.4 months (median)	Individuals aged over 18 years with no or stable pre-existing health conditions at high risk for contracting COVID-19 e.g. health and social care settings.	UK intervention group Age: 18-55 years: 79%, 56-69: 12%, ≥70: 9% Male: 42% Placebo: 18-55 years: 79%, 56-69: 12%, ≥70: 9% Male: 41% Brazil intervention group 18-55 years: 89%, 56-69: 10%, ≥70: 0.5% Male: 38.9% Placebo: 18-55 years: 90.5%, 56-69: 9%, ≥70: 0.2% Male: 42.9%	Type: replication deficient adenoviral vector vaccine containing the SARS-CoV-2 structural surface glycoprotein antigen (spike protein) gene Dose: 3.5-6.5 x 10^10 virus particles by qPCR assay Schedule: two doses, boost shots delivered 4-12 weeks after initial shot
Folegatti (2020)[24] UK	Phase I/II RCT 56 days	Healthy adults aged 18–66 years.	ChAdOx1 Male: 51% Age: 34 years (IQR 28, 43) MenACWY Male: 49% Age: 36 (IQR 28, 45)	Type: replication deficient adenoviral vector vaccine containing the SARS-CoV-2 structural surface glycoprotein antigen (spike protein) gene Dose: $5x10^5$ viral particles

Author (year) location	Setting Study design Follow-up	Eligibility criteria	Patient demographics	Vaccine information [a]
				Schedule: Two doses, 28 days
Moderna trials				
Jackson (2020)[25] USA	Phase I trial Single arm 57 days	Healthy adults 18–55 years, not screened for SARS-CoV-2 prior.	Age: 33.0 years (SD 8.5) Male: 49%	Type: mRNA vaccine Dose: 100 mcg Schedule: Two doses 28 days apart
Chu (2021)[26] USA	Phase II trial RCT 57 days	Healthy patients aged ≥ 18 years with BMI 18-30 kg/m^2 and no known history of SARS-CoV-2.	Cohort 1 18-54 years: Age: 37.5 (range 18–54) Male: 41% Cohort 2 (≥ 55 years) Age: 64.3 (range 55–87) Male: 29%	Type: mRNA vaccine Dose: 100 mcg Schedule: Two doses 28 days apart
Baden (2021)[27] USA	Phase III trial RCT 120 days	Patients ≥ 18 years with no known history of SARS-CoV-2, in locations or circumstances at increased risk of SARS-CoV-2 infection.	Intervention Age: 51.4 (range 18–95) Male: 52.2% Placebo Age: 51.3 (range 18–95) Male: 46.9%	Type: mRNA vaccine Dose: 100 mcg Schedule: Two doses 28 days apart
Novavax trials				
Keech (2020)[28] Australia	Phase I/II trial RCT 189 days	Healthy men or non-pregnant women, 18–59 years, BMI 17–35 kg/m^2. Patients with previous SARS-CoV-2 infection (or at high risk) were excluded.	Age: 30.8 years (SD 10.20) Male: 50.4%	Type: recombinant nanoparticle vaccine from wild-type SARS-CoV-2 with Matrix-1 (saponin-based adjuvant) Dose: 5 mcg + matrix 50 mcg Schedule: Two doses 21 days apart
Heath (2021)[29] UK	Phase III trial RCT 126 days	Healthy (or with stable chronic conditions) adults 18–84 years. Excluded were patients with a history of COVID-19 or those with an immunodeficiency condition.	Age: median 56 (IQR 18, 84) Male: 51.6%	Type: recombinant nanoparticle vaccine from wild-type SARS-CoV-2 with Matrix-1 (saponin-based adjuvant) Dose: 5 mcg + matrix 50 mcg Schedule: Two doses 21 days apart
Janssen trials				

Author (year) location	Setting Study design Follow-up	Eligibility criteria	Patient demographics	Vaccine information [a]
Sadoff (2021)[30] USA	Phase I/II trial RCT 71 days	Healthy adults	Cohort 1 18-55 years Age: 35.4 years (SD 10.2) Male: 47% Cohort 2 ≥ 65 years Age: 69.8 years (SD 4.0) Male: 50%	Type: recombinant, replication incomplete adenovirus encoding full length SARS-CoV-2 spike Dose: 5 x 10^10 viral particles Schedule: single dose
Sadoff (2021)[31] Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, USA	Phase III trial RCT 126 days	Adults ≥ 18 years	Age: 52[b] (range, 18–100) Male: 54.9%	Type: recombinant, replication incomplete adenovirus encoding full length SARS-CoV-2 spike Dose: 5 x 10^10 viral particles Schedule: single dose
Gamaleya trials				
Lugunov (2021)[32] Russia	Phase I/II trial RCT 42 days	Healthy adults (18-60 years, BMI 18.5–30 kg/m$^{2)}$ with negative PCR and antibodies to SARS-CoV-2 and no history of COVID-19.	Age: 26.7 years (SD 5.8) Male: 70%	Type: two adenoviral vector vaccines - recombinant AD26 and recombinant Ad5 Dose: 10^11 viral particles Schedule: Ad26 day 1, Ad5 day 22
Lugunov (2021)[33] Russia	Phase III trial RCT 180 days	Adults ≥ 18 years, negative SARS-CoV-2 PCR and antibody tests and no history of, or close contact with, COVID-19. Patients on steroids or immunosuppressants were excluded.	Vaccine group Age: 45.3 years (SD 12.0) Male: 61.1% Control group Age: 45.3 years (SD 11.9) Male: 61.5%	Type: two adenoviral vector vaccines - recombinant AD26 and recombinant Ad5 Dose: 10^11 viral particles Schedule: Ad26 day 1, Ad5 day 22
Sinovac trials				
Wu (2021)[34] China	Phase I/II trial Pseudo-RCT 28 days	Healthy adults > 60 years without a high risk of SARS-CoV-2 within 14 days of enrolment. Patient were	Vaccine Age: 66.5 (SD 4.9) Male: 51% Placebo	Type: Inactivated virus vaccine Dose: 3 µg Schedule: two doses 14 day apart

Author (year) location	Setting Study design Follow-up	Eligibility criteria	Patient demographics	Vaccine information [a]
		excluded if they had positive antibodies for SARS-CoV-2.	Age: 67.4 (SD 4.9) Male: 46%	
Tanriover (2021)[35] Turkey	Phase III trial RCT 120 days	Patients 18–59 years with no history of COVID-19. Patients using immunosuppressant therapy or Ig therapy and pregnant women were excluded.	Vaccine Age: 45 years[b] (IQR 37, 51) Male: 57.4% Control Age: 45 years (IQR 37, 51) Male: 58.6%	Type: Inactivated virus vaccine Dose: 3 µg Schedule: two doses 14 day apart
Palacios (2021)[36] Brazil	Phase III trial RCT 14 days	Healthcare professionals 18–59 years without previous SARS-CoV-2 infection.	Vaccine Age: 18-59 years (94.9%) Male: 36.6% Placebo Age: 18-59 (94.9%) Male: 35.0%	Type: Inactivated virus vaccine Dose: 3 µg Schedule: two doses 14 day apart
Sinopharm trials				
Kaabi (2021)[37] China	Phase III trial RCT 120 days	Healthy people >18 years, negative for SARS-CoV-2 antibodies without a known history of MERS or SARS-CoV-2 who had not travelled outside of China or to Hubei Province.	WIV04 strain Age: 36.2 years (SD 9.2) Male: 84% HB02 strain Age: 36.1 years (SD 9.3) Male: 84.5% Placebo Age: 36.1 years (SD 9.3) Male: 84.8%	Type: 2 versions of Inactivated SARS-CoV-2 vaccine (WIV04 and HBO2 strains) Dose: WIV04 5 µg, HB02 4 mcg Schedule: two doses 28 day apart

Abbreviations

HIV = human immunodeficiency virus, **IQR** = interquartile range, µg = microgram, **mRNA** = messenger ribonucleic acid, **NR** = not reported, **RCT** = randomised controlled trial, **SD** = standard deviation, **UK** = United Kingdom, **USA** = United States of America.

Notes

a = extraction was limited to details and results from the type, dose and schedule of each vaccine that was approved for use following phase III trials.

b = Median.

Table 11 Existing recommendations for COVID-19 vaccination and surgery

Organisation	Location	Publication type	Source of evidence	Timing of vaccination to surgery	Population	Recommendations	Date of recommendation/update
COVID-19 vaccine guidance							
American Society of Anesthesiologists[1]	USA	Webpage: FAQ/news	Expert opinion (likely)	Before	NR	'If you've been vaccinated, your surgery should be scheduled at least two weeks after your final dose so that you are fully protected.'	14/03/2021
American Society of Transplantation[2]	USA	Webpage: FAQ, guidance	NR	Before and after	Patients undergoing/ underwent transplant surgery	'For pre-transplant patients, we recommend vaccination completion at least 2 weeks prior to transplantation of possible. For post-transplant patients, we recommend administering vaccination beginning as early as 1-3 months after transplantation.'	17/05/2021
Arthritis and Musculoskeletal Alliance (includes British Orthopaedic Association, British Society for Rheumatology and Rare Autoimmune Rheumatic Disease Alliance)[3]	UK	Webpage: guidance	Expert opinion, literature review	Before and after	NR	'It is recommended that people undergoing elective surgery have 7 days between the vaccination and surgery (both before and after surgery). This applies to both doses of the vaccine.'	09/06/2021
Association of Anaesthetists, Centre for Perioperative Care, The Federation of Surgical Specialty Associations, Royal College of Anaesthetists and Royal College of Surgeons of England[4]	UK	Journal article: consensus statement	Expert opinion, systematic review	Before	NR	'SARS-CoV-2 vaccination of patients several weeks before hospital admission, where appropriate and as prioritised by national vaccination strategies.'	18/03/2021

Organisation	Location	Publication type	Source of evidence	Timing of vaccination to surgery	Population	Recommendations	Date of recommendation/update
Association of Paediatric Anaesthetists of Great Britain and Ireland[5]	UK	Webpage: guidance	Literature review	Before and after	Paediatric	'Inactivated vaccines – delay major elective surgery until 48 hours after vaccination because of the potential overlap between surgical complications and adverse effects of the vaccine.' 'Vaccines may be administered after elective surgery after the child has recovered and is well.'	16/03/2021
Australasian Society of Aesthetic Plastic Surgeons [TM 6]	Australia	Webpage: guidance	Expert opinion, existing guidelines	Before and after	NR	'It is recommended that the date of surgery is separated from the date of vaccination by at least one week.'	25/02/2021
Australasian Society of Clinical Immunology and Allergy[7]	Australia and New Zealand	Webpage: guidance/ position statement	Expert opinion, literature review	Before and after	NR	'… recommend that people do not have major surgery and vaccines within one week of each other.'	14/04/2021
Australian Rheumatology Association[8]	Australia	Webpage: NR	NR	Before and after	NR	'Surgery guidelines recommend people do not have major surgery and vaccines within one week of each other.'	09/04/2021
Australian and New Zealand College of Anaesthetists[9]	Australia and New Zealand	Webpage: news	Expert opinion	Before and after	NR	'It is recommended to not schedule COVID-19 vaccination within 1 week before elective surgery or 1 week after elective or non-elective surgery.'	08/06/2021
Bowel Cancer Australia [10]	Australia	Webpage: NR	NR	After	Patients with cancer	'Recommendations for COVID-19 vaccination based on cancer treatment: 1. Delay 1 to 2 weeks after major surgery.'	NR
COVID-19 Critical Intelligence Unit[11]	Australia	Report: NR	Systematic review	Before	Adults and paediatrics, patients undergoing/ underwent transplantation	Identified 7 publications. Recommendations ranged from a few days to 3–4 weeks post-vaccination.	20/05/2021

Organisation	Location	Publication type	Source of evidence	Timing of vaccination to surgery	Population	Recommendations	Date of recommendation/update
Hospitals of Cologne[12]	Germany	Journal article: guidance	Expert opinion, literature review	Before	NR	'We recommended delaying the highly elective procedure until 15 days after the second vaccine shot.'	20/03/2021
National Cancer Control Programme[13]	Ireland	Webpage: FAQs	NR	Before	Patients with cancer	'If possible, vaccines should be given at least 7 days before surgery to ensure that the side effects of the vaccine are not confused with other side effects related to your operation. However, in situations where this is not possible, the vaccine can be administered less than 7 days before surgery.'	12/07/2021
University Health Network[14]	Canada	Journal article: guidance	Expert opinion, literature review	Before and after	NR	'We recommend scheduling the COVID-19 vaccine at least one week before surgery so symptoms such as fever can be correctly attributed to side effects from the vaccine rather than surgery.' 'Vaccination can also occur once patients are recovered, one to two weeks after breast surgery.'	22/06/2021
Royal College of Surgeons of England[15]	UK	Webpage	NR	Before	NR	'Essential urgent surgery should take place, irrespective of vaccination status. Non-urgent elective surgery can also take place soon after vaccination. There is some rationale for separating the date of surgery from vaccination by a few days (at most 1 week) so that any symptoms such as fever might be correctly attributed to the consequences of either vaccination or the operation itself.'	22/01/2021
General vaccine guidance							

Organisation	Location	Publication type	Source of evidence	Timing of vaccination to surgery	Population	Recommendations	Date of recommendation/update
Association of Paediatric Anaesthetists of Great Britain and Ireland[16]	UK	Webpage/ report: guidance	Literature review	Before and after	Paediatrics	In children: Inactivated vaccines: 'delay surgery 48 hours post vaccination' Live attenuated: 'no reason to delay if child well at time of immediate preoperative assessment' 'No contraindication to vaccination immediately after surgery …'	16/03/2021
Centre for Disease Control[17]	USA	Webpage: practice guidelines	Literature review	Before and after	NR	'… anesthesia/surgery/hospitalization is not a contraindication to vaccination, but certain factors might lead a provider to consider current, recent or upcoming anesthesia/surgery/hospitalization as a precaution.'	
Department of Health[18]	Australia	Immunisation handbook: practice guidelines	Literature review	Before and after	Paediatrics	'If elective surgery and anaesthesia are to be postponed after vaccination, some guidelines recommend waiting for 1 week after receiving an inactive vaccine and for 3 weeks for receiving a live attenuated viral vaccine in children. Defer routine vaccines for 1 week after surgery.'	08/06/2018
Department of Health[19]	Australia	Immunisation handbook: practice guidelines	NR	After	NR	Blood transfusion products: interval 0–6 months Immunoglobulin products: interval: 0–11 months	05/06/2018

Abbreviations

NR = not reported, **UK** = United Kingdom, **USA** = United States of America.

Table 12 Local and systemic adverse events following COVID-19 vaccines (clinical trials)

	Vaccines approved in Aotearoa New Zealand and Australia						Vaccines approved internationally											
	AZD1222 AstraZeneca/ Oxford University [a 20]		BNT162b2 Pfizer (adults) [b 21]		BNT162b2 Pfizer (adolescents) [c 22]		Ad26COVS1 Jassen [d 23]		BIBP/WIBP Sinopharm [e 24]		CoronaVac Sinovac [f 25]		CoronaVac Sinovac [f 26]		mRNA-1273 Moderna [27]		NVX-CoV2373 Novavax [28]	
	V	P	V	P	V	P	V	P	V	P	V	P	V	P	V	P	V	P
Number of patients	487	477	8,183		2,260		3,356	3,380	13,464	13,453	6,202	6,202	6,646	3,568	15,168	15,155	2,310	
Local adverse events 1st dose																		
Pain	67%	38%	83%	14%	83%	16%	59%	18%	24%	28%	60%	33%	2%	1%	88%	17%	30%	10%
Redness	15%	10%	5%	1%	6%	1%	9%	5%	1%	1%	4%	1%	0.2%	0.1%	9%	0.4%	2%	1%
Swelling	21%	14%	6%	0%	8%	1%	7%	2%	2%	1%	6%	2%	<1%	<1%	12%	0.3%	1%	1%
2nd dose																		
Pain	50%	NR	78%	12%	78%	12%	NA		24%	28%	NR		NR		84%	18%	51%	8%
Redness	0%	NR	6%	1%	6%	0%	NA		1%	1%	NR		NR		3%	0.4%	7%	0%
Swelling	0%	NR	6%	0%	7%	0%	NA		2%	1%	NR		NR		6%	0.3%	5%	0%
Systemic adverse events 1st dose																		
Fever	87%	2%	4%	1%	7%	1%	12%	1%	2%	2%	0.2%	0.1%	2%	2%	16%	0.3%	2%	2% h
Fatigue	70%	48%	47%	33%	60%	39%	43%	21%	11%	11%	15%	15%	8%	7%	65%	23%	20%	18%
Headache	68%	41%	42%	34%	54%	37%	44%	35%	13%	13%	34%	34%	6%	6%	59%	23%	24%	21%
Chills	56%	10%	14%	6%	25%	9%	NR		NR		5%	5%	3%	2%	44%	6%	NR	
Vomiting/ Nausea	25%	10%	1%	1%	2%	2%	15%	8%	1%	1%	8%	8%	<1%	<1%	19%	6%	5%	5%
Diarrhoea	NR		11%	12%	11%	11%	NR		4%	4%	8%	8%	2%	2%	NR		NR	
Muscle pain	60%	25%	21%	11%	27%	14%	39%	11%	5%	5%	12%	11%	4%	3%	58%	12%	22%	14%
Joint pain	31%	10%	11%	6%	13%	5%	NR		1%	1%	5%	5%	<1%	<1%	43%	11%	2%	2%
2nd dose																		
Fever	70%	NR	16%	0%	17%	0%	NA		2%	2%	NR		NR		0.5%	0.3%	4%	0%
Fatigue	50%	NR	59%	23%	66%	23%	NA		11%	11%	NR		NR		37%	27%	40%	14%

	Vaccines approved in Aotearoa New Zealand and Australia						Vaccines approved internationally								
	AZD1222 AstraZeneca/ Oxford University [a 20]		BNT162b2 Pfizer (adults) [b 21]		BNT162b2 Pfizer (adolescents) [c 22]		Ad26COVS1 Jassen [d 23]	BIBP/WIBP Sinopharm [e 24]		CoronaVac Sinovac [f 25]	CoronaVac Sinovac [f 26]	mRNA-1273 Moderna [27]		NVX-CoV2373 Novavax [28]	
Headache	70%	NR	52%	24%	61%	24%	NA	13%	13%	NR	NR	33%	27%	39%	17%
Chills	80%	NR	35%	4%	40%	4%	NA	NR		NR	NR	8%	6%	NR	
Vomiting/ Nausea	40%	NR	3%	1%	3%	2%	NA	1%	1%	NR	NR	8%	7%	9%	2%
Diarrhoea	NR		10%	8%	8%	4%	NA	4%	4%	NR	NR	NR		NR	
Muscle pain	60%	NR	37%	8%	41%	10%	NA	6%	6%	NR	NR	22%	14%	40%	8%
Joint pain	30%	NR	22%	5%	22%	4%	NA	2%	1%	NR	NR	16%	12%	16%	4%

Abbreviations

NA = not applicable, **NR** = not reported, **P** = placebo or control group, **V** = COVID-19 vaccine group.

Notes

a = Phase II clinical trials for the AstraZeneca/Oxford University did not report local or systemic reactogenicity, results are informed from phase their I/II trial.[20] Only 10 patients in the phase I/II trials received prime and boost vaccinations. Non-paracetamol group reported. The phase III trial noted, 'A lower-than-anticipated reactogenicity profile was noted in the trial'.[29]

b = Data presented for 16-55 year old cohort.

c = The reactogenicity subset included all 12- to 15-year-old participants and a subset of 16- to 25-year-old participants. 16-25-year-old data presented. Incidence of local and systemic reactogenicity was generally similar between age groups.

d = Results obtained from webplotdigitizer. Data presented for 18- to 59-year-old.

e = WIV04 vaccine reported. HB02 vaccine was broadly similar with respect to adverse events (albeit lower number of patients of pain reported, 19.4%). Nausea reported. 2nd dose = 0–28 days, may include patients who reported event between 0–7 days.

f = Adverse reactions after first or second dose of vaccine or placebo.

g = Phase III clinical trials for the Gamaleya vaccine did not report local or systemic reactogenicity. The authors noted, 'The most common adverse events were flu-like illness, injection site reactions, headache, and asthenia'.

h = Results obtained from webplotdigitizer, and incidence of fever was informed by 'elevated temperature'.

Table 13 Local and systemic adverse events following COVID-19 vaccines (vaccine safety surveillance databases)

	Active surveillance databases				**Passive surveillance databases** [a]						
	Australia Pfizer [b 30]	**Australia AstraZeneca** [b 30]	**USA Pfizer** [c 31]	**USA Moderna** [c 31]	**Aotearoa New Zealand Pfizer** [d 32]	**Canada Pfizer** [e 33]	**Canada Moderna** [e 33]	**Canada AstraZeneca** [e 33]	**UK Pfizer** f 34	**UK Moderna** [f 35]	**UK AstraZeneca** [f 36]
Number of patients or doses	1st dose 756,844 2nd dose 531,147	1st dose 399,883 2nd dose 132,339	1st dose 1,659,724 2nd dose 971,375	1st dose 1,984,194 2nd dose 777,264	1,229,212 doses	31,280,396 doses	11,350,147 doses	2,761,580 doses	33,300,00 doses	1,300,000 doses	47,900,000 doses
Number of adverse event reports	NA	NA	NA	NA	6,145	6,036	3,238	1,389	95,040	10,990	224,252
Local adverse events 1st dose											
Pain	29.9%	19.7%	64%	71%	0.10%	0.005%	0.02%	0.60%	0.005%	0.01%	0.004%
Redness	NR	NR	3%	7%	NR	0.002%	0.02%	0.30%	0.001%	0.01%	0.001%
Swelling	4.5%	NR	7%	14%	NR	0.002%	0.02%	0.31%	0.001%	0.008%	0.001%
2nd dose											
Pain	43.0%	15.3%	67%	78%	-	-	-	-	-	-	-
Redness	NR	NR	6%	19%	-	-	-	-	-	-	-
Swelling	NR	NR	10%	26%	-	-	-	-	-	-	-
Systemic adverse events 1st dose											
Fever	NR	17.5%	7%	10%	0.11%	0.003%	0.006%	0.85%	0.02%	0.09%	0.11%
Fatigue	20.5%	42.2%	29%	33%	NR	0.005%	0.006%	0.77%	0.04%	0.1%	0.1%
Headache	15.5%	35.6%	24%	27%	0.18%	0.006%	0.007%	1.52%	0.05%	0.1%	0.2%
Chills	4.8%	26.3%	7%	10%	NR	0.002%	0.004%	0.72%	0.02%	0.05%	0.09%
Nausea	NR	NR	7%	8%	0.12%	0.005%	0.007%	0.67%	0.03%	0.07%	0.07%
Diarrhoea	NR	NR	5%	5%	NR	0.002%	0.003%	0.31%	0.011%	0.02%	0.02%
Muscle pain	11.3%	31.2%	17%	21%	0.05%	0.002%	0.003%	0.39%	0.02%	0.05%	NR
Joint pain	5.0%	19.7%	7%	10%	0.05%	0.002%	0.003%	0.36%	0.00008%	0.003%	0.0001%
2nd dose											
Fever	13.4%	4.4%	22%	38%	-	-	-	-	-	-	-

	Active surveillance databases				Passive surveillance databases [a]						
	Australia Pfizer [b 30]	**Australia AstraZeneca** [b 30]	**USA Pfizer** [c 31]	**USA Moderna** [c 31]	**Aotearoa New Zealand Pfizer** [d 32]	**Canada Pfizer** [e 33]	**Canada Moderna** [e 33]	**Canada AstraZeneca** [e 33]	**UK Pfizer** [f 34]	**UK Moderna** [f 35]	**UK AstraZeneca** [f 36]
Fatigue	43.3%	19.0%	48%	60%	-	-	-	-	-	-	-
Headache	33.6%	15.6%	50%	53%	-	-	-	-	-	-	-
Chills	21.8%	7.1%	23%	40%	-	-	-	-	-	-	-
Nausea	NR	NR	13%	20%	-	-	-	-	-	-	-
Diarrhoea	NR	NR	6%	8%	-	-	-	-	-	-	-
Muscle pain	33.0%	11.9%	37%	51%	-	-	-	-	-	-	-
Joint pain	18.3%	7.2%	20%	32%	-	-	-	-	-	-	-

Abbreviations

NA = not applicable, **NR** = not reported, **UK** = United Kingdom, **USA** = United States of America.

Notes

a = For passive surveillance reports, the incidence of adverse events was obtained by dividing the number of adverse events by the number of doses administered. The incidence per first or second dose could not be obtained because the studies only reported total doses administered.

b = AusVaxSafety, accessed 31/07/2021, results reported as of 25/07/2021.[30]

c = Chapin-Bardales (2021), based on vaccine event reporting system (Centre for Disease Control and Prevention) results obtained from 14/12/2020 to 28/02/2021.[31]

d = Medsafe, accessed 31/07/2021, results reported as of 3/07/2021. [32]

e = Health Canada, accessed 31/07/2021, results reported as of 23/07/2021.[33]

f = Medicines & Healthcare products Regulatory Agency (yellow card), accessed 31/07/2021, results reported as of 21/07/2021.[34-36]

Table 14 Background incidence of adverse event of special interest per 100,000 person years (Li 2021)[37]

AESI category	AESI	Sex	Incidence rate Event per 100,000 person years (95% CI) 16 to 34 years 35 to 54 years	Incidence rate Event per 100,000 person years (95% CI) 55 to 64 years ≥85 years
Immune system disorders	Guillain-Barre syndrome	Female	3 (1 to 5) 3 (1 to 11)	5 (1 to 18) 7 (2 to 22)
		Male	2 (1 to 4) 4 (2 to 7)	7 (4 to 14) 12 (2 to 68)
	Immune thrombocytopenia	Female	14 (6 to 36) 15 (5 to 43)	18 (6 to 53) 36 (11 to 118)
		Male	8 (2 to 23) 10 (3 to 35)	19 (6 to 57) 56 (15 to 210)
	Disseminated intravascular coagulation	Female	4 (<1 to 99) 5 (<1 to 75)	10 (1 to 89) 16 (3 to 82)
		Male	4 (<1 to 31) 5 (1 to 56)	12 (1 to 120) 24 (5 to 126)
	Anaphylaxis	Female	39 (16 to 95) 34 (13 to 91)	35 (14 to 85) 12 (4 to 36)
		Male	29 (14 to 63) 24 (11 to 53)	25 (11 to 53) 10 (2 to 50)
Cardiovascular system	Acute myocardial infarction	Female	6 (1 to 49) 54 (7 to 430)	171 (24 to 1235) 1144 (313 to 4184)
		Male	16 (4 to 72) 172 (40 to 740)	467 (135 to 1611) 1514 (356 to 6432)
	Myocarditis or pericarditis	Female	16 (8 to 32) 22 (9 to 53)	31 (13 to 72) 34 (8 to 143)
		Male	37 (16 to 88) 37 (16 to 87)	45 (20 to 102) 41 (9 to 193)
Blood and lymphatic system	Non-haemorrhagic stroke	Female	18 (4 to 86) 83 (11 to 617)	217 (25 to 1882) 1523 (230 to 7239)
		Male	17 (4 to 75)	379 (67 to 2046)

AESI category	AESI	Sex	Incidence rate Event per 100,000 person years (95% CI) 16 to 34 years 35 to 54 years	Incidence rate Event per 100,000 person years (95% CI) 55 to 64 years ≥85 years
			119 (21 to 664)	1495 (260 to 8607)
	Pulmonary embolism	Female	38 (11 to 124) 81 (21 to 309)	125 (33 to 470) 427 (154 to 1184)
		Male	20 (5 to 80) 80 (20 to 318)	171 (59 to 497) 398 (124 to 1277)
	Haemorrhagic stroke	Female	13 (4 to 47) 36 (7 to 175)	77 (15 to 389) 412 (85 to 1986)
		Male	19 (5 to 76) 51 (10 to 268)	115 (23 to 562) 506 (86 to 2961)
	Deep vein thrombosis	Female	140 (66 to 298) 306 (117 to 797)	428 (150 to 1224) 1206 (407 to 3572)
		Male	80 (28 to 228) 272 (88 to 836)	499 (194 to 1289) 1003 (278 to 3616)
Nervous system	Narcolepsy	Female	15 (4 to 52) 11 (2 to 55)	9 (2 to 42) 9 (2 to 42)
		Male	13 (4 to 40) 10 (2 to 47)	11 (3 to 44) 10 (2 to 60)
	Transverse myelitis	Female	3 (1 to 8) 4 (1 to 12)	4 (2 to 13) 2 (1 to 9)
		Male	2 (1 to 6) 3 (1 to 10)	4 (1 to 10) 4 (1 to 11)
	Encephalomyelitis	Female	5 (2 to 19) 6 (1 to 44)	9 (1 to 61) 14 (2 to 100)
		Male	5 (2 to 17) 7 (1 to 55)	12 (3 to 58) 16 (1 to 180)
	Bell's palsy	Female	44 (23 to 84) 61 (26 to 140)	76 (31 to 184) 92 (31 to 274)
		Male	43 (29 to 64)	86 (43 to 172)

AESI category	AESI	Sex	Incidence rate Event per 100,000 person years (95% CI) 16 to 34 years 35 to 54 years	Incidence rate Event per 100,000 person years (95% CI) 55 to 64 years ≥85 years
			68 (37 to 125)	100 (34 to 292)
Other	Appendicitis	Female	134 (69 to 260) 85 (42 to 172)	66 (28 to 156) 35 (12 to 98)
		Male	146 (81 to 266) 88 (49 to 159)	65 (32 to 132) 45 (14 to 143)

Abbreviation

AESI = adverse event of special interest, **CI** = confidence interval.

Notes

Council for International Organizations of Medical Sciences (CIOMS) thresholds: very common (≥1/10), common (<1/10 to ≥1/100), uncommon (<1/100 to ≥1/1,000), rare (<1/1,000 to ≥1/10,000), and very rare (<1/100,000).

Source

Li (2021)[37]

Table 15 Serious treatment-related adverse events (AESI) following COVID-19 vaccination (phase II/III trials)

AESI category	AESI	AZD1222 AstraZeneca/ Oxford University [20]		BNT162b2 Pfizer (adolescents) [22]		Ad26COVS1 Janssen [23]		BIBP/WIBP Sinopharm [24]		mRNA-1273 Moderna [27]		NVX-CoV2373 Novavax [28]	
	Treatment group	V	P	V	P	V	P	V	P	V	P	V	P
	Number of patients	12,021	11,724	3,000	3,035	21,895	21,888	13,464	13,453	15,185	15,166	7,569	7,570
Immune system	Guillain-Barre syndrome					1 <0.1%	0 0%						
	Anaphylaxis			0 0%	0 0%							0 0%	0 0%
Cardiovascular system	Myocarditis/pericarditis					1 <0.1%	0 0%					1 <0.1%	0 0%
Blood and lymphatic system	Pulmonary embolism									0 0%	1 <0.1%		
	Deep vein thrombosis			0 0%	0 0%	1 <0.1%	1 <0.1%						
Nervous system	Bell's palsy					2 <0.1%	0 0%						
	Acute disseminated encephalomyelitis							1 <0.1%	0 0%				
	Transverse myelitis	1 <0.1%	0 0%										

Abbreviations

AESI = adverse event of special interest, **P** = placebo or control group, **V** = COVID-19 vaccine group.

Notes

No treatment-related adverse events were reported for Gamaleya,[38] Pfizer (adults),[21] and Sinovac.[25]

Table 16 Serious adverse events following COVID-19 vaccination (phase II/III trials)

AESI Category	AESI	AZD1222 Astra-Zeneca/ Oxford University Interim [29]		AZD1222 Astra-Zeneca/ Oxford University [39]		BNT162b2 Pfizer adults [21]		BNT162b2 Pfizer adolescents [22]		Ad26COVS1 Jassen [23]		BIBP/WIBP Sinopharm [24]		Corona-Vac Sinovac [25]		CoronaVac Sinovac [26]		Gam-COVID-Vac Gamaleya [38]		mRNA-1273 Moderna [27]		NVX-CoV2373 Novavax [28]	
		V	P	V	P	V	P	V	P	V	P	V	P	V	P	V	P	V	P	V	P	V	P
	Number of patients	12,021	11,724	12,282	11,962	21,720	21,728	3,000	3,035	21,895	21,888	13,464	13,453	6,195	6,201	6,646	3,568	16,427	5,435	15,185	15,166	7,569	7,570
Immune system	Guillain-Barre Syndrome									1 <0.1 %	1 <0.1 %												
	Anaphyl-axis	1 <0.1 %	0 0%					0 0%	0 0%											1 <0.1 %	1 <0.1 %	0 0%	0 0%
Cardiovascular system	Myocardial infarction			1 <0.1 %	1 <0.1 %											0 0%	1 <0.1 %	2 0.01 %	1 0.02 %	5 <0.1 %	3 <0.1 %		
	Myocarditis/pericarditis			1 <0.1 %	2 <0.1 %																	1 <0.1 %	0 0%
	Atrial fibrillation																	3 0.02 %	1 0.02 %	5 <0.1 %	5 <0.1 %		
	Coronary artery disease							0 0%	0 0%											2 <0.1 %	2 <0.1 %		
Blood and lymphatic system	Pulmonary embolism	1 <0.1 %	0 0%	0 0%	1 <0.1 %					4 <0.1 %	1 <0.1 %									4 <0.1 %	5 <0.1 %		
	Deep vein thrombosis	0 0%	1 <0.1 %							6 <0.1 %	2 <0.1 %			1 <0.1 %	0 0.0 %			1 0.006%	0 0.0 %	2 <0.1 %	0 0.0 %		

AESI Category	AESI	AZD1222 Astra-Zeneca/ Oxford University Interim [29]		AZD1222 Astra-Zeneca/ Oxford University [39]		BNT162b2 Pfizer adults [21]		BNT162b2 Pfizer adolescents [22]		Ad26COVS1 Jassen [23]		BIBP/WIBP Sinopharm [24]		Corona-Vac Sinovac [25]		CoronaVac Sinovac [26]		Gam-COVID-Vac Gamaleya [38]		mRNA-1273 Moderna [27]		NVX-CoV2373 Novavax [28]	
Hepato-gastrointestinal and renal system	Acute kidney injury			1 <0.1 %	0 0%															1 <0.1 %	3 <0.1 %		
	Pancreatitis			3 <0.1 %	0 0%													1 0.006%	0 0%				
Nervous system	Bell's palsy	3 <0.1 %	3 <0.1 %							3 <0.1 %	2 <0.1 %									3 <0.1 %	1 <0.1 %		
	Transverse myelitis	1 <0.1 %	0 0%	1 <0.1 %	0 0%							1 <0.1 %	0 0.0 %										
	General convulsions/seizure	0 0%	1 <0.1 %							4 0.02 %	1 <0.1 %					1 <0.1 %	0 0%			2 <0.1 %	0 0%		
	Stroke	1 <0.1 %	0 0%	1 <0.1 %	0 0%					1 <0.1 %	0 <0.1 %							0 0.0 %	1 0.02 %	3 <0.1 %	1 <0.1 %		
Pregnancy, puerperium and perinatal conditions	Spontaneous abortion			2 <0.1 %	1 <0.1 %													0 0%	1 0.2 %				
Infections and musculoskeletal	Appendicitis			6 <0.1 %	7 <0.1 %			1 <0.1 %	1 <0.1 %					5 0.1 %	1 <0.1 %			1 0.006%	2 0.04 %	2 <0.1 %	3 <0.1 %		
	Rhabdomyolysis			0 0%	1 <0.1 %																		

Abbreviations

AESI = adverse event of special interest, **P** = placebo or control group, **V** = COVID-19 vaccine group.

Table 17 Adverse events of special interest following COVID-19 vaccination (total events by country)

AESI Category		Total number of events				Events per 100,000 doses			
		Aotearoa New Zealand [32]	**Australia [40 41]**	**Canada [42]**	**UK [34-36]**	**Aotearoa New Zealand [32]**	**Australia [40 41]**	**Canada [42]**	**UK [34-36]**
	Vaccine doses administered	***1,229,212***	***10,100,000***	***44,694,799***	***80,900,000***	***1,229,212***	***10,100,000***	***44,694,799***	***80,900,000***
	AESI								
Immune system	Guillain-Barré Syndrome	<6	61	53	412	<0.49	2.7	0.12	0.51
	Thrombocytopenia	<6	34	67	1,017	<0.49	1.5	0.15	1.26
	Thrombosis with thrombocytopenia syndrome	0	87	67	426	0	1.8 - 3.3	0.15	0.53
	Anaphylaxis	21	154	137	1,059	1.71	1.52	0.3	1.31
Cardio-vascular system	Myocardial infarction	<6	22	54	535	<0.49	0.22	0.12	0.66
	Myocarditis/pericarditis	12	66	230	454	0.98	1.65	0.51	0.56
	Heart failure	NR	2	14	121	NR	0.02	0.03	0.15
	Arrhythmia	NR	15	NR	228	NR	0.15	NR	0.28
	Coronary artery disease	NR	1	NR	10	NR	0.01	NR	0.01
Blood and lymphatic system	Thrombosis	<6	45	137	1,929	<0.49	0.44	0.3	2.38
	Embolism	10	149	212	1,570	0.81	1.47	0.47	1.94
	Deep vein thrombosis	11	161	136	1,314	0.89	1.59	0.3	1.62
	Vasculitis	<6	2	7	150	<0.49	0.02	0.02	0.19
	Haemorrhage	21	6	31	2,009	1.71	0.06	0.07	2.48
	Disseminated intravascular coagulation	NR	1	NR	19	NR	0.01	NR	0.02
	Microangiopathy	NR	NR	NR	1	NR	NR	NR	0.001

AESI Category		Total number of events				Events per 100,000 doses			
		Aotearoa New Zealand [32]	**Australia [40 41]**	**Canada [42]**	**UK [34-36]**	**Aotearoa New Zealand [32]**	**Australia [40 41]**	**Canada [42]**	**UK [34-36]**
	Vaccine doses administered	***1,229,212***	***10,100,000***	***44,694,799***	***80,900,000***	***1,229,212***	***10,100,000***	***44,694,799***	***80,900,000***
Respiratory system	Acute respiratory distress syndrome	NR	NR	2	3	NR	NR	0	0.004
Hepato-gastrointestinal and renal system	Acute kidney injury	0	6	19	94	0	0.06	0.04	0.12
	Acute liver injury	<6	2	10	28	<0.49	0.02	0.02	0.03
	Acute pancreatitis	NR	4	NR	27	NR	0.04	NR	0.03
	Appendicitis	NR	5	NR	59	NR	0.05	NR	0.07
Nervous system	Aseptic meningitis	0	NR	NR	1	0	NR	NR	0.001
	Encephalitis	0	NR	NR	52	0	NR	NR	0.06
	Acute disseminated encephalomyelitis	NR	1	NR	7	NR	0.01	NR	0.009
	Stroke	13	49	104	1,420	1.06	0.48	0.23	1.76
	Bell's Palsy/facial paralysis	19	20	291	892	1.55	0.2	0.64	1.1
	Myelitis	0	1	18	81	0	0.01	0.04	0.1
	Generalized convulsion	NR	46	NR	1,703	NR	0.45	NR	2.11
	Subacute thyroiditis	NR	NR	NR	5	NR	NR	NR	0.006
Infections and musculoskeletal	Erythema multiforme	0	2	13	69	0	0.02	0.03	0.09
	Arthritis	<6	11	NR	666	<0.49	0.11	NR	0.82
	Herpes zoster	33	68	NR	2,620	2.68	0.67	NR	3.24
	Chilblain-like lesions	NR	3	7	127	NR	0.03	0.02	0.16
	Rhabdomyolysis	NR	2	NR	17	NR	0.02	-	0.02
Pregnancy, puerperium	Abortion (spontaneous abortion /miscarriage)	NR	5	20	386	NR	0.05	0.02	0.48

AESI Category		Total number of events				Events per 100,000 doses			
		Aotearoa New Zealand [32]	**Australia [40 41]**	**Canada [42]**	**UK [34-36]**	**Aotearoa New Zealand [32]**	**Australia [40 41]**	**Canada [42]**	**UK [34-36]**
	Vaccine doses administered	***1,229,212***	***10,100,000***	***44,694,799***	***80,900,000***	***1,229,212***	***10,100,000***	***44,694,799***	***80,900,000***
and perinatal conditions									
Other	Anosmia and ageusia	NR	50	NR	1,905	NR	0.49	NR	2.35

Abbreviations

AZ = AstraZeneca, **NR** = not reported, **P** = Pfizer, **UK** = United Kingdom.

Notes

a = Events reported for AstraZeneca as of 22 July 2021.

b = Events reported for AstraZeneca and Pfizer as of May 2021.

c = Events reported for Pfizer only as of 22 July 2021.

The incidence of stroke, embolism, generalised convulsion and haemorrhage was informed by cerebrovascular accident, pulmonary embolism, seizures and cerebral haemorrhage from Australian, Canadian and UK databases.

Source

Aotearoa New Zealand, Medsafe,[32] accessed 29/07/2021, results reported as of 3/07/2021.

Australia, TGA weekly safety report[40] and DAEN database,[41] accessed 29/07/21, results reported as of 22/07/2021 and May 2021, respectively.

Canada, Health Canada,[33] date accessed 29/07/21, results reported as of 23/07/2021.

UK, MHRA,[34-36 43] date accessed 29/07/21, results reported as of 21/07/2021.

Table 18 Adverse events of special interest following COVID-19 vaccination (total events by manufacturer)

		Total number of events						Events per 100,000 doses					
	Country	**Canada** [42]	**UK** [34-36]	**Canada** [42]	**UK** [34-36]	**Canada** [42]	**UK** [34-36]	**Canada** [42]	**UK** [34-36]	**Canada** [42]	**UK** [34-36]	**Canada** [42]	**UK** [34-36]
	Manufacturer	***AstraZeneca***		***Moderna***		***Pfizer***		***AstraZeneca***		***Moderna***		***Pfizer***	
	Vaccine doses administered	***2,761, 580***	***32,100, 000***	***11,350, 147***	***1,300, 000***	***31,280, 396***	***32,100, 000***	***2,761, 580***	***32,100, 000***	***11,350, 147***	***1,300, 000***	***31,280, 396***	***32,100, 000***
	AESI												
Immune system	Guillain-Barré Syndrome	25	372	8	2	20	38	0.91	0.78	0.07	0.15	0.06	0.12
	Thrombocytopenia	45	851	5	11	15	155	1.63	1.79	0.04	0.85	0.05	0.48
	Thrombosis with thrombocytopenia syndrome	56	411	2	0	9	15	2.03	0.87	0.02	0	0.03	0.05
	Anaphylaxis[b]	0	657	24	23	113	379	0	1.38	0.21	1.77	0.36	1.18
Cardio-vascular system	Myocardial infarction	8	376	13	9	32	150	0.29	0.79	0.11	0.69	0.1	0.47
	Myocarditis/pericarditis	12	202	71	37	145	215	0.43	0.43	0.62	2.84	0.46	0.67
	Heart failure	3	73	2	1	9	47	0.11	0.15	0.02	0.07	0.03	0.15
	Arrhythmia	NR	132	NR	5	NR	91	NR	0.28	NR	0.38	NR	0.28
	Coronary artery disease	NR	6	NR	NR	NR	4	NR	0.01	NR	NR	NR	0.01
	Thrombosis	69	1595	8	40	58	294	2.5	3.36	0.07	3.08	0.19	0.92

		Total number of events						Events per 100,000 doses					
	Country	**Canada** [42]	**UK** [34-36]	**Canada** [42]	**UK** [34-36]	**Canada** [42]	**UK** [34-36]	**Canada** [42]	**UK** [34-36]	**Canada** [42]	**UK** [34-36]	**Canada** [42]	**UK** [34-36]
	Manufacturer	***AstraZeneca***		***Moderna***		***Pfizer***		***AstraZeneca***		***Moderna***		***Pfizer***	
	Vaccine doses administered	***2,761, 580***	***32,100, 000***	***11,350, 147***	***1,300, 000***	***31,280, 396***	***32,100, 000***	***2,761, 580***	***32,100, 000***	***11,350, 147***	***1,300, 000***	***31,280, 396***	***32,100, 000***
Blood and lymphatic system	Embolism	91	1498	1	10	2	62	3.3	3.15	0.01	0.77	0.01	0.19
	Deep vein thrombosis	49	1107	22	10	65	197	1.77	2.33	0.19	0.77	0.21	0.61
	Vasculitis	0	110	3	1	4	39	0	0.23	0.03	0.077	0.01	0.12
	Haemorrhage	8	1268	7	99	16	642	0.29	2.67	0.06	7.62	0.05	2
	Disseminated intravascular coagulation	NR	17	NR	NR	NR	2	NR	0.036	NR	NR	NR	0.006
	Microangiopathy	NR	NR	NR	NR	NR	1	NR	NR	NR	NR	NR	0.003
Respiratory system	Acute respiratory distress syndrome	0	1	1	NR	2	2	0	0.002	0.01	NR	0.01	0.006
Hepato-gastrointestinal and renal system	Acute kidney injury	1	58	4	2	14	34	0.04	0.12	0.03	0.15	0.04	0.11
	Acute liver injury	2	20	2	NR	6	8	0.07	0.04	0.02	NR	0.02	0.02
	Acute pancreatitis	NR	18	NR	NR	NR	9	NR	0.04	NR	NR	NR	0.03
	Appendicitis	NR	35	NR	2	NR	22	NR	0.07	NR	0.15	NR	0.07
Nervous system	Aseptic meningitis	NR	NR	NR	NR	NR	1	NR	NR	NR	NR	NR	0.003

		Total number of events						Events per 100,000 doses					
	Country	**Canada** [42]	**UK** [34-36]	**Canada** [42]	**UK** [34-36]	**Canada** [42]	**UK** [34-36]	**Canada** [42]	**UK** [34-36]	**Canada** [42]	**UK** [34-36]	**Canada** [42]	**UK** [34-36]
	Manufacturer	***AstraZeneca***		***Moderna***		***Pfizer***		***AstraZeneca***		***Moderna***		***Pfizer***	
	Vaccine doses administered	***2,761, 580***	***32,100, 000***	***11,350, 147***	***1,300, 000***	***31,280, 396***	***32,100, 000***	***2,761, 580***	***32,100, 000***	***11,350, 147***	***1,300, 000***	***31,280, 396***	***32,100, 000***
	Encephalitis	NR	38	NR	NR	NR	14	NR	0.08	NR	NR	NR	0.04
	Acute disseminated encephalomyelitis	NR	3	NR	NR	NR	4	NR	0.006	NR	NR	NR	0.01
	Stroke	29	1114	15	7	58	299	1.05	2.35	0.13	0.54	0.19	0.9
	Bell's Palsy/facial paralysis	36	527	63	26	191	339	1.3	1.11	0.55	2	0.61	1.06
	Myelitis	4	77	3	NR	11	4	0.14	0.16	0.03	NR	0.04	0.01
	Generalized convulsion	NR	1250	NR	55	NR	398	NR	2.63	NR	4.23	NR	1.24
	Subacute thyroiditis	NR	3	NR	NR	NR	2	NR	0.006	NR	NR	NR	0.006
Infections and musculoskeletal	Erythema multiforme	1	36	3	9	9	24	0.04	0.08	0.03	0.69	0.03	0.07
	Arthritis	NR	484	NR	7	NR	175	NR	1.02	NR	0.54	-	0.54
	Herpes zoster	NR	1494	NR	27	NR	1099	NR	3.15	NR	2.07	-	3.42
	Chilblain-like lesions	0	72	1	6	6	49	0	0.15	0.01	0.46	0.02	0.15
	Rhabdomyolysis	NR	9	NR	1	NR	7	NR	0.02	NR	0.07	-	0.02

		Total number of events						Events per 100,000 doses					
	Country	**Canada** [42]	**UK** [34-36]	**Canada** [42]	**UK** [34-36]	**Canada** [42]	**UK** [34-36]	**Canada** [42]	**UK** [34-36]	**Canada** [42]	**UK** [34-36]	**Canada** [42]	**UK** [34-36]
	Manufacturer	***AstraZeneca***		***Moderna***		***Pfizer***		***AstraZeneca***		***Moderna***		***Pfizer***	
	Vaccine doses administered	***2,761, 580***	***32,100, 000***	***11,350, 147***	***1,300, 000***	***31,280, 396***	***32,100, 000***	***2,761, 580***	***32,100, 000***	***11,350, 147***	***1,300, 000***	***31,280, 396***	***32,100, 000***
Pregnancy, puerperium and perinatal conditions	Abortion (spontaneous abortion /miscarriage)	0	171	4	18	16	197	0	0.36	0.03	1.38	0.05	0.61
Other	Anosmia and ageusia	NR	1338	NR	25	NR	542	NR	2.81	NR	1.92	NR	1.69

Abbreviations

NR = not reported.

Notes

The incidence of stroke, embolism, generalised convulsion and haemorrhage was informed by cerebrovascular accident, pulmonary embolism, seizures and cerebral haemorrhage from Canadian and UK databases.

Source

For the incidence of AESI from Aotearoa New Zealand, Medsafe see ***Table 17***.

In Australia, the number of doses administered per vaccine manufacturer could not be determined and hence the incidence was not reported.

Canada, Health Canada,[33] date accessed 29/07/21, results reported as of 23/07/2021.

UK, MHRA,[34-36 43] date accessed 29/07/21, results reported as of 21/07/2021.

Table 19 Onset of AESI following COVID-19 vaccines

Body system	AESI	Level of evidence Number of patients	Vaccine manufacturer	Median (range) time from COVID-19 vaccine to AESI
Immune system	Guillain-Barre syndrome	IV (case series/reports)[44-46] n = 6	AstraZeneca	13 days (10–14 days)
	Thrombocytopenia	IV (regulator database, VAERS)[47] n = 23	Moderna, Pfizer	5.5 days (1–23 days)
	Thrombosis with thrombocytopenia syndrome	IV (regulatory databases TGA, Health Canada)[33 40] n = 154	AstraZeneca	Australia: 12 days (1–51 days) Canada: NR (1–34 days)
	Anaphylaxis [b]	IV (regulatory database Health Canada)[42] n = 32	Moderna, Pfizer	66% of cases occurred within 15 mins (2–180 mins)
Cardiovascular system	Myocardial infarction	IV (case report)[48-50] n = 3	AstraZeneca, Moderna, Pfizer	1h (0.5–2 hrs)
	Myocarditis/pericarditis	IV (regulatory databases TGA, Health Canada)[33 40] n = 296	Moderna, Pfizer	Australia: most within 14 days Canada: 1 hour–94 days
	Heart failure	IV (case series)[51]	Moderna	6hrs
	Arrhythmia	No information on onset		
	Coronary artery disease	No information on onset		
Blood and lymphatic system	Thrombosis	See thrombosis and thrombocytopenia		
	Embolism	IV (case report)[52-57] n = 6	AstraZeneca, Janssen, Pfizer	8.5 days (6–28 days)
	Deep vein thrombosis	IV (case reports)[52 58 59] n = 4	AstraZeneca, Pfizer	17 days (2–29 days)
	Vasculitis	IV (case reports)[60-67] n = 9	AstraZeneca, Bharat, Moderna, Pfizer	4 days (2–28 days)
	Haemorrhage	IV (case report)[68] n = 1	Moderna	3 days

	Disseminated intravascular coagulation	IV (case series)[69-71] n = 3	AstraZeneca	12 days (2–14 days)
	Microangiopathy	IV (case report)[72] n = 1	AstraZeneca	11 days
Respiratory system	Acute respiratory distress syndrome	IV (case report)[73] n = 1	NR	14 days
Hepato-gastrointestinal and renal system	Acute kidney injury	IV (case report)[74 75] n = 2	AstraZeneca, Pfizer	10 and 13 days
	Acute liver injury	IV (case report)[76] n = 1	Pfizer	12 days
	Acute pancreatitis	IV (case reports)[77 78] n = 2	Pfizer	20hrs
	Appendicitis	No evidence on onset		
Nervous system	Aseptic meningitis	IV (case report)[79] n = 1	Pfizer	7 days
	Encephalitis	IV (case reports)[80 81] n = 2	AstraZeneca, Moderna	1 and 5 days
	Acute disseminated encephalomyelitis	IV (case report)[82-84] n = 3	Pfizer, Sinopharm, Sinovac	14 days (14–30 days)
	Stroke	IV (case series)[85-94] n = 42	AstraZeneca, Pfizer	9 days (3–21 days)
	Bell's palsy/facial paralysis	II,[95] III (case-control),[96] IV (case series/report)[97-100] n = 33	Janssen, Moderna, Pfizer	19.5 days (1.5–48 days, n = 12) 9.3 days (3–14 days, n = 21)[96]
	Myelitis	II[29] and IV (case report)[101 102] n = 3	AstraZeneca, Sinovac	14 days (11–14 days)
	Generalised convulsion	IV (case series/reports)[103-105] n = 4	AstraZeneca, Pfizer	4 days (1–10 days)
	Subacute thyroiditis	IV (case series/reports)[106 107] n = 4	AstraZeneca, Sinovac	5.5 days (4–21 days)
Infections and musculoskeletal	Erythema multiforme	IV (case reports)[108 109] n = 2	Pfizer, Sinovac	0.5 and 5 days
	Arthritis	IV (report)[110] n = 1	Sinovac	4 days

	Herpes zoster	IV (case series/reports)[111-119] n = 70	AstraZeneca, Bharat, Moderna, Pfizer	5-6 days (1–10 days)
	Chillblain-like lesions	IV (case series/reports) [120-126] n = 8	Moderna, Pfizer, Sinovac	5.5 days (1–12 days)
	Rhabdomyolysis	IV (case series/reports)[127 128] n = 2	Pfizer, Moderna	1 and 2 days
Pregnancy, puerperium and perinatal conditions	Abortion (spontaneous abortion/miscarriage)	No information on onset		
Other	Anosmia and ageusia	No information on onset		

Notes

Cases of transverse myelitis in [101] and [29] confounded by pre-existing MS, and MenACWY vaccination.[29] Those deemed not related to the COVID vaccine were not included.

For acute kidney injury, first symptom was oedema. [74 75]

The incidence of embolism, stroke, deep vein thrombosis and haemorrhage was often secondary to TTS.

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