Interim report 2021

COVID-19 Vaccine Independent Safety Monitoring Board (CV-ISMB)

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Table of Contents

Definitions

Adverse Event Following Immunisation (AEFI)
An AEFI is an untoward medical event which follows immunisation and does not necessarily have a causal relationship with the administration of the vaccine. The adverse event may be an unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.

Adverse events of special interest (AESI)
An AESI is a pre-specified medically significant event that has the potential to be causally associated with the vaccine product based on past experience, the technology used to make the vaccine or the infection the vaccine is used to protect against. AESIs need to be carefully monitored and any potential association to vaccination confirmed by further analysis and studies.

Safety signal
Information on a new or known adverse event that may be caused by the vaccine and requires further investigation. Safety signals can be detected from a wide range of sources such as AEFI reports, clinical studies and scientific literature.

Serious adverse event following immunisation
An AEFI is considered serious if it:

- is a medically important event or reaction
- requires hospitalisation or prolongs an existing hospitalisation
- causes persistent or significant disability or incapacity
- is life threatening
- causes a congenital anomaly/birth defect
- results in death.

It is possible for different people to have experienced the same event but for the report to be serious for one person and non-serious for another person, depending on the impact or outcome of the event in each person.

Causality assessment
Systematic review and evaluation of available data about the AEFI to determine the likelihood of a causal association between the event(s) and the vaccine received.

1 Overview

Cases investigated (up to 28 November 2021)

The AstraZeneca COVID-19 vaccine is not included in this overview because the data thus far is extremely limited, and an update will be provided in the new year (see Section 7).

Number of AEFIs reported in the COVID CARM database: **39,973**
Number of Pfizer/BioNTech doses administered: **7,498,139**

Total number of serious cases reported to COVID CARM	Serious cases presented to CV-ISMB	Safety signals investigated
1,593	**508**	**18**

Type of incidents reported

AEFI type	**Number reported**	**Cases presented to CV-ISMB***
Hospitalisation	662	187
Medically Significant	543	123
Died	123	123
Life Threatening	91	45
Persisting Disability	149	27
Congenital effect	3	3
Non-serious	38,379	227

*Cases presented to CV-ISMB have been primarily for signal review. Individual events have not been evaluated by the Board for causality.

CV-ISMB meetings

Members recruited	16
Meetings held	16
Number of recommendations	28

NOTE: Given that more than 3.7 million people in New Zealand have been vaccinated, a number of medical events will occur coincidentally in the period following vaccination and this should be taken into consideration when reading this report.

1.1 Introduction

In 2020, the New Zealand government secured advanced purchase agreements for a portfolio of four different COVID-19 vaccines (Pfizer/BioNTech, AstraZeneca, Janssen and Novavax), with a view for delivery to the population in 2021.

The COVID-19 Vaccine and Immunisation Programme (CVIP) is delivering New Zealand's largest ever immunisation programme, to vaccinate as many eligible people as possible throughout 2021. The COVID-19 vaccine rollout commenced in New Zealand in February 2021 with the Pfizer/BioNTech vaccine.

The CVIP's purpose is to make the best use of any vaccines, to support the immediate health response and to help achieve the COVID-19 vaccine strategy longer-term outcomes which include:

- sufficient supply of a safe and effective vaccine to achieve population immunity to COVID-19, affordably
- protection for Māori, Pacific peoples, and population groups at particular risk from COVID-19
- full cultural, social and economic recovery from the impacts of COVID-19
- recognition of New Zealand as a valued contributor to global wellbeing and the COVID-19 response
- New Zealand, Pacific and global preparedness for response to future disease outbreaks.

The COVID-19 Vaccine Independent Safety Monitoring Board (CV-ISMB) was established in February 2021. The purpose and function of the Board is to provide expert advice on the safety of the COVID-19 vaccine(s) to the Centre for Adverse Reactions Monitoring (CARM), Medsafe, the CVIP and the Ministry of Health during the rollout across Aotearoa New Zealand.

Seven Pacific countries have been offered access to New Zealand's vaccine portfolio: Fiji, the three Realm countries (Cook Islands, Niue and Tokelau), and Samoa, Tonga and Tuvalu. The Board is also providing support to these countries if requested.

Key areas of focus for the Board include:

- support with assessment of potential causal links between reported adverse events following immunisation (AEFI) and COVID-19 vaccines
- review of all serious and significant AEFI for the COVID-19 vaccines that are presented for expert opinion (this includes all fatal reports)
- advice to Medsafe and the CVIP in relation to the balance of benefits and risks for potential safety signals under investigation and whether further action is needed
- ensuring that equity is a key consideration for the collection, monitoring and reporting of AEFI for the COVID-19 vaccines.

Further detailed information about the role/function, composition, workplan, reporting and duties/responsibilities of the Board and its members is available within the Terms of Reference (Appendix 1).

1.2 Members

The Chair and other members of the Board are drawn from experts in various fields of clinical medicine, biostatistics, microbiology and immunology. The Board also holds a position for a lay member (non-healthcare professional) to represent the interests of the consumer. The composition of the CV-ISMB is as follows:

- a neurologist
- two general practitioners (one in urban practice, one in rural practice)
- a cardiologist
- a clinical pharmacologist
- two biostatisticians
- a haematologist
- a paediatrician
- a consumer
- a general medicine specialist
- two immunologists
- a clinical microbiologist
- an obstetrician and gynaecologist
- a rheumatologist.

The Chairperson of the COVID-19 Vaccine Technical Advisory Group (CV-TAG) is an ex-officio (non-voting) member of the Board and attends meetings to provide a link between CV-TAG and the CV-ISMB. The Director of the New Zealand Pharmacovigilance Centre (NZPhvC) attends meetings to present case details to the Board. Technical experts from Medsafe and the CVIP also attend to present information on safety signals under investigation and other safety surveillance work for the COVID-19 vaccines.

1.2.1 Chair and Deputy Chair

Mr John Tait (Chair) *(MB, MS, FRCOG, FRANZCOG)*
Mr Tait is an obstetrician and gynaecologist who has worked in Wellington since 1986. He is the current Chief Medical Officer at Capital & Coast and Hutt Valley District Health Boards. Prior to this role he was the Executive Director Clinical, Surgery, Women's and Children's. Mr Tait is the Chair of the Perinatal & Maternal Mortality Review Committee (PMMRC), Vice President of the Asia and Oceania Federation of Obstetricians and Gynaecologists (AOFOG) and an ex-officio member of the National Maternity Monitoring Group. Mr Tait provides expertise in the field of obstetrics.

Honorary Associate Professor Hilary Longhurst (Deputy Chair) *(MA, FRCP(UK), PhD, FRCPath)*
Dr Longhurst is a clinical immunologist at Auckland District Health Board. She has extensive experience in treating allergic and immunological problems, with particular interests in immune deficiency, rare angioedemas and telomere biology disorders. Throughout her career, she has worked closely with patient groups on research aimed at developing better treatments and improving health for those with rare immunological disorders. Dr Longhurst provides expertise in the field of immunology, including those with immune deficiency and allergy.

1.2.2 Current members

Dr Nick Cutfield *(MBChB, FRACP, MD(RES))*
Dr Cutfield is the Clinical Director of Neurology and Clinical Neurophysiology at Southern District Health Board. He is a Clinical Senior Lecturer at the Dunedin School of Medicine, University of Otago. Dr Cutfield is the Director of the New Zealand Creutzfeldt-Jakob Disease surveillance registry and the Director of the Brain Research New Zealand Dementia Prevention Research Clinic (Dunedin). He was previously the Clinical Deputy Director of the University of Otago Brain Health Research Centre and Member of the Neurological Foundation of New Zealand Scientific Advisory Committee. Dr Cutfield provides expertise in the field of neurology.

Associate Professor Matt Doogue *(BSc, MBChB, DipPaeds, FRACP)*
Associate Professor Doogue is a clinical pharmacologist, Clinical Director of the Department of Clinical Pharmacology at the Canterbury District Health Board (CDHB) and a physician on general medicine at CDHB. He is a clinical academic at the University of Otago, Christchurch, with interests including adverse drug reactions, clinical decision support, therapeutic drug monitoring and medical education. He is vice-chair of the International Union of Basic and Clinical Pharmacology (IUPHAR) clinical division. Dr Doogue provides expertise in the field of clinical pharmacology.

Dr Kyle Eggleton *(BHB, MBChB, MMedSci, MPH, PhD, DipObstMedGyn, DipPaeds, DIH, FRNZCGP(Dist))*
Dr Eggleton is a rural general practitioner at Hauora Hokianga in Northland. He is also Associate Dean of Rural Health at the University of Auckland. Dr Eggleton has worked as a general practitioner in rural Whangārei, Ruakākā and Rawene, mostly working for Māori health providers. He sits on a number of governance boards including the Northland District Health Board. Dr Eggleton provides expertise in the field of rural general practice and equity.

Professor Chris Frampton *(BSc Hons, PhD)*
Professor Frampton is a part time biostatistician within the departments of Psychological medicine and Medicine at the University of Otago, Christchurch. He is a member of the Standing Committee on Therapeutic Trials (SCOTT), the PHARMAC Cancer Treatments Subcommittee (CaTSoP) and the Medicines Assessment Advisory Committee (MAAC). Professor Frampton is a member of the invited faculty for the Australasian Clinical Oncology Research Development (ACORD) and the international Collaboration for Research Development in Oncology (CREDO) workshops, run biennially in Australia and annually in India. His specific research focus is on the design, conduct and analysis of randomised controlled trials (RCTs) and he serves on many international data safety monitoring committees overseeing multi-national RCTs. Professor Frampton provides expertise in the field of biostatistics.

Dr Maryann Heather *(BHB, MBChB, MAvMed, DipOccMed, PGCertTravMed, PGCertHsC(SportsMed), FRNZCGP)*
Dr Heather is a general practitioner working at Etu Pasifika Auckland. She has worked in Australia, Samoa, American Samoa, and China. She is also an emerging Pacific Health researcher and Senior Lecturer in Pacific Health at the School of Population Health, Faculty of

Medical and Health Sciences, University of Auckland, and a GP teacher and student supervisor in Pacific Health, Public Health and General Practice. She is a member of the Pacific GP network, Pacific Chapter Royal New Zealand College of General Practitioners (RNZCGP), executive committee member Auckland Faculty RNZCGP, Goodfellow Unit Advisory Board Member (Pacific), Pasifika Medical Association Governance Membership Board (Director), Influenza Working Group (Pacific and Primary Care), RUAG Pharmac (Medicines Equity in Primary Care - Pacific), COVID-19 Pacific Response media team, Science Media Centre advisory team (Pacific), NZ Breast Cancer Foundation Medical Advisory Committee (Primary Care and Pacific), Health Research Council (HRC) Co-opted panel assessment committee (Primary Care and Pacific). Dr Heather brings expertise in Primary Care, Pacific Health and Health Equity.

Dr Tom Hills *(MBChB, MSc, DPhil, FRACP)*
Dr Tom Hills is a University of Otago-trained clinical immunologist, with a doctorate in rapid response vaccine design from the University of Oxford. His clinical work is in Auckland, with a research appointment at the Medical Research Institute of New Zealand in Wellington. Dr Hills provides expertise in the fields of immunology and clinical trials.

Professor Thomas Lumley *(PhD, FRSNZ)*
Professor Lumley is the Chair in Biostatistics in the Department of Statistics at the University of Auckland and an Affiliate Professor in the Department of Biostatistics at the University of Washington. He has a wide range of research interests in theoretical and applied biostatistics. Professor Lumley also chairs the HRC Data Monitoring Core Committee, which provides data monitoring to publicly funded clinical trials in New Zealand. He is a Fellow of the Royal Society of New Zealand and of the American Statistical Association. Professor Lumley provides expertise in biostatistics.

Ms Saskia Schuitemaker *(MSocSc, PGDipPsych(Comm))*
Ms Schuitemaker is the Coordinator of the Child and Mortality Review Group (CYMRG) under the Māori, Equity and Health Improvement Directorate at the Waikato District Health Board. She was previously employed as a Health Consumer Service Facilitator of health consumer complaints. Ms Schuitemaker served as a lay member representing consumer interests on the Waikato Medical Ethics Committee for six years. She is also informed by her work as a Community Magistrate and Community Development Advisor. Ms Schuitemaker is a lay member (non-health professional) who provides a consumer lens.

Dr Owen Sinclair *(MBChB, MPH, FRACP)*
Dr Sinclair is a consultant General Paediatrician and Paediatric Emergency Medicine specialist working at Waitakere District Health Board. He is of Māori descent (Te Rarawa). He lectures in Māori health at the University of Auckland and is the lead for the Māori support network of Te Kāhui Mātai Arotamariki o Aotearoa, the Paediatric Society of New Zealand. He has completed research looking into ethnic inequalities in health, including vaccine preventable disease in children, and Māori attitudes to immunisation. He has given multiple presentations on the causes of ethnic inequalities in health in New Zealand and overseas. Dr Sinclair provides expertise in the fields of paediatrics and Māori health.

Professor Lisa Stamp *(MBChB, PhD, DipMus, FRACP)*
Professor Stamp is a consultant rheumatologist at Christchurch Hospital and an academic rheumatologist and Associate Dean of Research at the University of Otago, Christchurch. She is Director of the Canterbury Rheumatology and Immunology Research Group. Professor Stamp provides a rural clinic in Kaikōura and is a member of PHARMAC's Pharmacology and Therapeutics Advisory Committee (PTAC). Her research interests include gout and rheumatoid arthritis, and she has published over 170 papers in these areas. Professor Stamp received the Value of Medicines NZ prize in 2017 for her world leading work in the use of allopurinol. Professor Stamp provides expertise in the field of rheumatology.

Honorary Professor Ralph Stewart *(MD, FRACP, FCSANZ, FESC)*
Dr Stewart is a cardiologist at Auckland City Hospital and the Auckland Heart Group, and an Honorary Professor of Medicine at the University of Auckland. He is past Chairman of the New Zealand Division of the Cardiac Society of Australia and New Zealand, and of the National Cardiac Network, and is a member of a number of national and international cardiology and research organisations. Dr Stewart provides expertise in the field of cardiology.

Dr Anja Werno *(MD, PhD, MBA, FRCPA, FFSc)*
Dr Werno was born and raised in Germany where she graduated in medicine in 1993. She was granted her Microbiology Fellowship (Royal College of Pathologists of Australasia, RCPA) in 2004. Dr Werno's longstanding research interest is reflected in an MD in the field of HIV (University of the Saarland, Germany), her PhD in the field of invasive pneumococcal disease (University of Otago), and her recent admission as a Fellow of the Faculty of Science (RCPA) on the grounds of scientific achievement. Since the start of the SARS-CoV-2 pandemic, Dr Werno has been a member of the Ministry of Health's Science and Technical Advisory Expert Network. From 2017 to 2020 she chaired the NZ Microbiology Network and was a nominated representative on Australia's Public Health Laboratory Network (PHLN). She is currently employed as a clinical microbiologist, the Acting Clinical Director of Microbiology and Chief of Pathology & Laboratories at Canterbury Health Laboratories and as a Clinical Senior Lecturer at the Christchurch School of Medicine, University of Otago. Dr Werno provides expertise in the fields of microbiology and pathology.

Dr Laura Young *(MBChB, PhD, FRACP, FRCPA)*
Dr Young is a clinical haematologist at Auckland District Health Board (ADHB) with an honorary lecturer appointment at the University of Auckland. She works predominantly in the Thrombosis Unit and Haemophilia Centre in Cancer and Blood at ADHB. She has a PhD and has clinical and translational research interests in this area. Dr Young provides expertise in the field of haematology.

Dr Enver Yousuf *(BSc, MB BS, Dip Pharm Med, FFPM)*
Dr Yousuf obtained his medical degree in the United Kingdom (UK) in 1994 and has worked in New Zealand (NZ) since 2008. He is an expert in pharmaceutical medicine and is a Fellow of the Faculty of Pharmaceutical Medicine of the Royal College of Physicians UK. He has experience working on medicine and vaccine safety in NZ and internationally. Dr Yousuf provides expertise in the field of general medicine and pharmaceutical medicine.

1.2.3 Conflicts of interest

The European Medicines Agency (EMA) policy on the handling of competing interests of scientific committees' members and experts was used to determine conflicts of interest prior to a member's appointment to the Board, and for participation in subsequent meetings (where required).

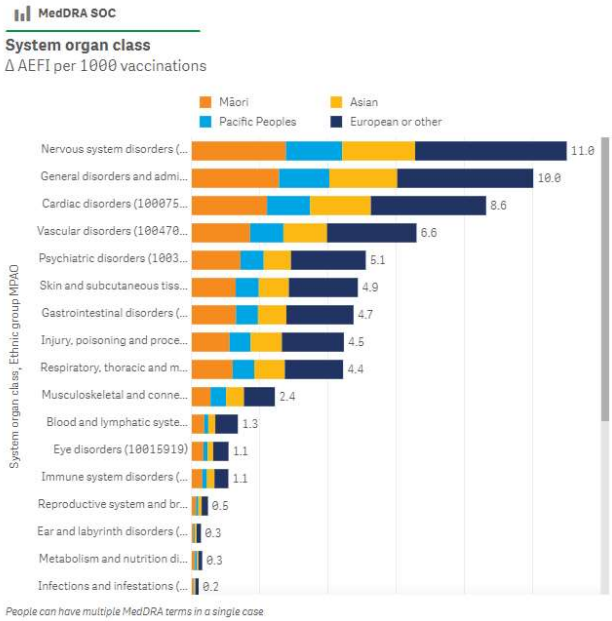
1.3 Equity

A primary focus of the Board is to ensure that equity is a key consideration in the collection, monitoring and reporting of AEFI to uphold the Crown's commitment to Te Tiriti o Waitangi and achieving equitable health outcomes for all people in Aotearoa New Zealand.

The Board includes expertise to represent the interests of Māori and Pasifika. The Board also includes two general practitioners (one in urban practice and one in rural practice), along with a lay member (non-healthcare professional) to represent the interests of the consumer.

An overview of AEFI reporting is regularly provided to the Board, with consideration given to reporting by ethnicity, age, gender and geographic location. Qlik Applications are being utilised to allow visualisation of safety data for the COVID-19 vaccines. Following feedback from the Board, the Qlik application for AEFI reporting was updated to allow standardisation of reported AEFI by ethnicity for events reported. An example of this is provided in Figure 1 below.

Figure 1: Visualisation from Qlik app of reported AEFIs per 1000 vaccinations by systemic organ class and ethnicity.



Source: Ministry of Health Qlik app. Data extracted 28 November 2021.

2 Safety signals investigated

A safety signal is information on a new or known adverse event that may be caused by the vaccine and requires further investigation. Safety signals can be detected from a wide range of sources such as CARM reports, clinical studies and scientific literature.

The assessment of safety signals establishes if there is a causal relationship between the vaccine and the reported adverse event.

As part of the assessment and evaluation of a safety signal, Medsafe considers:

- cases reported to CARM
- relevant information in the literature
- observed versus expected analysis if background rate is available
- Safety Reports the sponsor
- information from other international regulatory authorities.

Safety signals for the COVID-19 vaccines are presented and discussed with the CV-ISMB. Recommendations from the Board can include:

- continuing to monitor through routine pharmacovigilance
- Monitoring communication from Medsafe
- Alert communication from Medsafe
- updating the label (data sheet and consumer medicine information)
- holding or stopping the immunisation programme.

To date, Medsafe has evaluated 18 safety signals for the Pfizer/BioNTech vaccine. Once recommendation(s) have been made and implemented, safety signal investigations are considered closed. An investigation can be re-opened if needed, for example, if there is an increase in the number of reported cases (ie, menstrual disorders or unexpected vaginal bleeding) or further information is obtained from other regulatory agencies and the sponsor (ie, myocarditis). Table 1 provides a summary of these investigations, including information on the number of times a safety signal has been discussed by the Board, the outcome of the investigation, the most recent date it was presented to the Board, and any resulting recommendations/actions.

Table 1. Summary of investigations into possible safety signals

Safety signal (no. of times presented to board)	Outcome	most recent time considered	Cases reviewed	Explanation	Regulator action
Thrombosis with thrombocytopenia syndrome (TTS) (1)	Unlikely association. Continue to monitor. See also the Monitoring communication.	22/04/21	0	The Board was reassured by the international experience with the Pfizer/BioNTech vaccine which has been widely used in several countries, and the local experience in New Zealand to date, which did not identify a risk with the Pfizer/BioNTech vaccine. A Monitoring communication was recommended to reassure people that Medsafe is aware of the association between TTS and the Janssen and AstraZeneca COVID-19 vaccines. The safety of the Pfizer/BioNTech vaccine is being monitored closely for this issue.	Y
Appendicitis (1)	Unlikely association. Continue to monitor.	27/05/21	1	The Board agreed that current evidence does not suggest a safety signal for appendicitis, and that Medsafe should continue monitoring through routine pharmacovigilance activities.	N
Anaphylaxis (6)	Associated with any vaccine. Continue to monitor. Implement anaphylaxis checklist.	24/06/21	41	The Board agreed that if the numbers continue to track similarly (around 10 cases per million doses) that there is no need to continue to review in this forum.	Y
Pancreatitis (1)	Possible association. Continue to monitor.	24/06/21	1	The Board noted the individual had a previous history of pancreatitis, which is a known risk factor for future episodes. The Board acknowledged that it is not always going to be possible to determine the underlying cause of some events.	N
AEFIs in the elderly (1)	Unlikely association. Continue to monitor. Data sheet updated.	21/07/21	N/A*	The Board noted that even if elderly have limited life expectancy, vaccination can still help protect both the individual and those around them. It was also noted that most elderly who are competent to consent are willing to be vaccinated. Given there is no clear signal indicating that death is a consequence of vaccination, it is important to ensure they have the opportunity to be vaccinated. The Board recommended wording be included in the data sheet around consideration of the risk/benefit profile for vaccination of frail elderly consumers.	Y

Safety signal (no. of times presented to board)	Outcome	most recent time considered	Cases reviewed	Explanation	Regulator action
Seizure (1)	Unlikely association. Continue to monitor.	21/07/21	31	The Board agreed that the current data does not suggest a safety signal for seizures, and that Medsafe should continue monitoring through routine pharmacovigilance activities.	N
Tinnitus (1)	Unlikely association. Continue to monitor.	25/08/21	34	The Board noted that tinnitus occurs commonly in the general population, with the underlying cause in most cases remaining unknown. The description of tinnitus can vary between people and may be observed more frequently in individuals with anxiety due to heightened awareness. It was agreed that the current evidence did not present a concern at this stage, but that Medsafe should continue monitoring through routine pharmacovigilance activities.	N
Glomerular diseases (1)	Unlikely association. Continue to monitor.	25/08/21	15	The Board agreed that there was no particular concern at this stage regarding glomerular disease, and that Medsafe should continue monitoring through routine pharmacovigilance activities.	N
Guillain-Barré Syndrome (GBS) (1)	Possible association. Continue to monitor.	25/08/21	3	The Board agreed that current evidence does not suggest a safety signal for GBS. Some cases are expected to occur in the weeks following vaccination due to the background incidence of GBS. Medsafe should continue monitoring through routine pharmacovigilance activities.	N
Thrombocytopenia (1)	Possible association. Continue to monitor.	25/08/21	5	The Board agreed that the data at this stage is reassuring, with low case numbers, and that Medsafe should continue monitoring through routine pharmacovigilance activities.	N
Thrombosis (blood clots) (2)	Unlikely association. Continue to monitor.	04/10/21	121	The Board agreed that current evidence does not suggest a safety signal for thrombosis, and that Medsafe should continue monitoring through routine pharmacovigilance activities.	Y
Myocarditis/pericarditis (7)	Associated with the vaccine. Information has been added to Comirnaty data sheet. See also the Alert communication	27/10/21	10	Myocarditis has been shown nationally and internationally to be a rare side effect of the Pfizer/BioNTech vaccine, with current evidence suggesting most cases are mild and self-limiting. Given that COVID-19 induces myocarditis at a higher rate than the vaccine, the risk/benefit consideration is still in favour of vaccination. Medsafe and the Board continue to monitor this issue closely.	Y

Safety signal (no. of times presented to board)	Outcome	most recent time considered	Cases reviewed	Explanation	Regulator action
Menstrual disorder (2)	Unlikely association. Continue to monitor. See also the Monitoring communication.	27/10/21	9	The Board noted that due to how commonly menstrual disorders occur in the population generally, the most convincing data comes from the clinical trials where there is a control group. The Board discussed the merits of providing communications to the public to give reassurance that menstrual disorders have not been found to be linked to vaccination and any changes that occur after vaccination are likely to be temporary, with no evidence to suggest these temporary changes will impact on fertility.	Y
Pregnancy related outcomes (1)	Unlikely association. Continue to monitor. See the Monitoring communication.	27/10/21	2	The Board noted the concerning data emerging from the UK relating to COVID-19 infection (Delta variant) in unvaccinated pregnant woman, with several cases resulting in stillbirth. In contrast, the current data does not suggest any association between the vaccine and miscarriage or congenital abnormalities. The Board recommended a communication be issued advising that the available information for the use of the Pfizer/BioNTech vaccine in pregnancy had been reviewed with no safety concerns identified.	Y
Stroke (2)	Unlikely association. Continue to monitor.	17/11/21	80	The Board agreed that current evidence does not suggest a safety signal for stroke, and that Medsafe should continue monitoring through routine pharmacovigilance activities.	N
Erythema multiforme (1)	Unlikely association. Continue to monitor.	17/11/21	10	The Board agreed that current evidence does not suggest a safety signal for erythema multiforme, and that Medsafe should continue monitoring through routine pharmacovigilance activities.	N
Herpes zoster (2)	Probable association. Continue to monitor.	15/12/21	46	The Board agreed that current evidence does not suggest a safety signal for herpes zoster, and that Medsafe should continue monitoring through routine pharmacovigilance activities.	N
AEFIs in children (12+) (2)	Unlikely association. Continue to monitor	15/12/21	N/A*	The Board agreed that the current data does not suggest a safety concern for AEFIs in children (12+), and that Medsafe should continue monitoring through routine pharmacovigilance activities.	N

*Rather than looking at individual cases, these presentations focussed on overall trends within these groups. Cases are included in reviews for other safety signal investigations where applicable.

2.1 Anaphylaxis

Hypersensitivity to the active ingredient or to any of the excipients is the only contraindication for the Pfizer/BioNTech vaccine (Comirnaty). In addition, the data sheet includes the following warning and precaution for hypersensitivity and anaphylaxis, as below.

> *Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of COMIRNATY.*
>
> *The individual should be kept under close observation for at least 15 minutes following vaccination. A second dose of COMIRNATY should not be given to those who have experienced anaphylaxis to the first dose of COMIRNATY.*

The Board considered anaphylaxis in their first few meetings. Early in the vaccine rollout, when only a small number of people had been vaccinated, CARM had received three potential reports of anaphylaxis. This gave a reporting rate of 3 reports per 20,000 doses given. From a clinical perspective, these events had been managed appropriately. However, anaphylaxis is a rare post-vaccination event for other vaccines, with a reporting rate of 3 to 5 cases per million doses given.

On 11 March 2021, the Board recommended that all potential anaphylaxis reports be assessed against the Brighton Collaboration Criteria for anaphylaxis to determine whether a reaction constitutes anaphylaxis. The Anaphylaxis Tabular Checklist (Appendix 2) was presented to the Board by CARM as a proposed mechanism to evaluate reported cases of anaphylaxis for the CVIP. The checklist incorporates the Brighton criteria and allows for the collection of detailed information at the time of the event to support medical assessment. The checklist was endorsed by the Board as a useful document, and this was implemented by CARM. In a memo to the CVIP Steering Group on 7 May 2021, the Board recommended that consideration be given to the checklist being made available at vaccination sites. This was agreed and implemented by the CVIP.

In subsequent meetings (April to June), CARM provided an overview of the anaphylaxis reports received to date, including Brighton level, dose number, and time to onset. On 24 June 2021, the Board considered the rate of anaphylaxis according to the case definition (Brighton level 1-3). They noted that this data was reassuring, with a similar rate as that reported by the Centers for Disease Control (CDC) in the United States (US). The Board recommended that CARM should continue to monitor reports of anaphylaxis and only bring this safety issue back to the Board if there is a spike in reporting, or unusual cases reported.

2.2 Myocarditis

Myocarditis was first presented and discussed with the Board on 27 May 2021, at which point CARM had received two case reports of potential myocarditis in association with the Pfizer/BioNTech vaccine. At this time there was limited overseas data, with other regulatory agencies continuing to investigate. The sponsor's evaluation had not identified myocarditis as a potential safety signal, and they were continuing to monitor the concern. The Board recommended that Medsafe continue to monitor this closely. Medsafe published a Monitoring Communication issued on 9 June 2021, to provide reassurance and encourage reporting of any suspected myocarditis cases following the Pfizer/BioNTech vaccine.

A further update was provided to the Board on 24 June 2021, based on data from the CDC. The data showed young males in the US were experiencing higher rates of myocarditis than expected for the 12 to 24 years (significantly higher) and 25 to 39 years (slightly higher) age groups, with more reactions occurring after the second dose. There was also a higher rate of myocarditis for females following the second dose in the 12 to 24 years age group, however this wasn't as pronounced as the difference observed in males. The CDC had conducted rapid cycle analyses for myocarditis/pericarditis following administration of mRNA COVID-19 vaccines (Moderna and Pfizer/BioNTech) and concluded that the benefits clearly outweighed the risks.

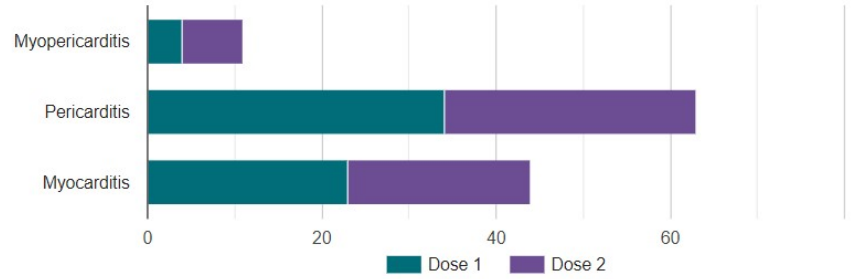
On 21 July 2021, Medsafe published an Alert communication for myocarditis and pericarditis as rare adverse reactions of the Pfizer/BioNTech vaccine. Based on international evidence and cases of myocarditis and pericarditis reported in New Zealand following the Pfizer/BioNTech vaccine, the data sheet and consumer medicine information were updated on 28 July 2021 to include myocarditis and pericarditis as rare adverse events, as below.

Very rare cases of myocarditis and pericarditis have been observed following vaccination with COMIRNATY. These cases have primarily occurred within 14 days following vaccination, more often after the second vaccination, and more often in younger men. Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination. Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

The Board continues to receive regular updates from Medsafe on the number of myocarditis and pericarditis cases (including myopericarditis) reported in New Zealand, with analysis of trends by dose, age range of individuals, and time to onset. As reported in Medsafe's COVID-19 Vaccine Safety Report #33, up to 14 October 2021, CARM had received 61 reports of clinically confirmed myocarditis or pericarditis after dose one and 57 reports after dose two. The number of reports is shown in Figure 2 below.

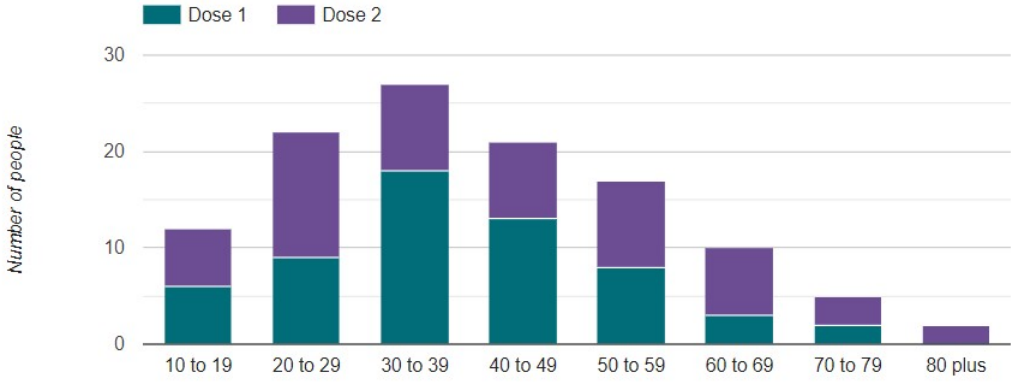
Figure 2. Number of reports of myocarditis and pericarditis after dose 1 and dose 2 of the Pfizer/BioNTech vaccine, up to 14 October 2021



Source: Medsafe. 2021. *Adverse events following immunisation with COVID-19 vaccines: Safety Report #33 – 16 October 2021*. URL: https://www.medsafe.govt.nz/COVID-19/safety-report-33.asp.

In 61 reports the sex was noted as female, and male in 57 reports. Ethnicity, when reported, was 84% European or other, 10.5% Asian, 4.5% Māori and 1% Pacific Peoples. The age of those reported to have experienced myocarditis or pericarditis after dose 1 or dose 2 is shown in Figure 3.

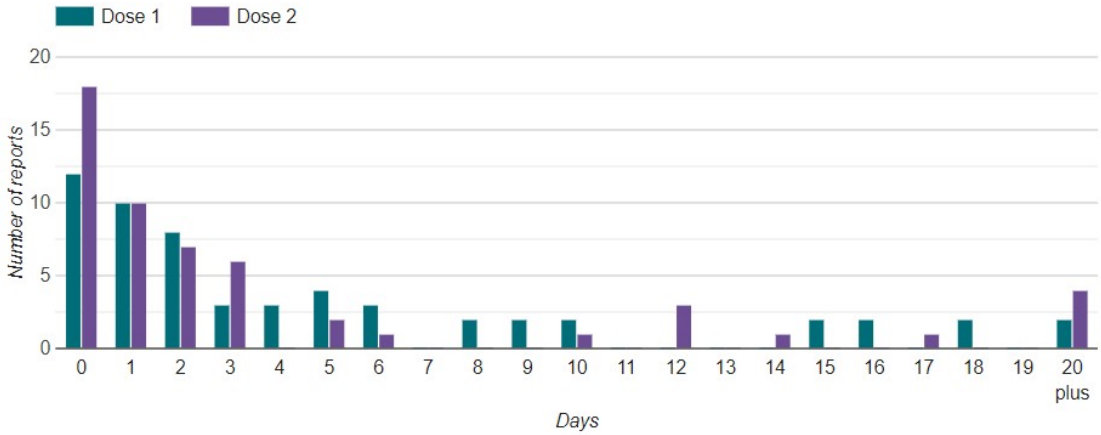
Figure 3. Age range of people reported to have experienced myocarditis or pericarditis after vaccination, up to 14 October 2021



Source: Medsafe. 2021. *Adverse events following immunisation with COVID-19 vaccines: Safety Report #33 – 16 October 2021*. URL: https://www.medsafe.govt.nz/COVID-19/safety-report-33.asp.

The time between vaccination and the first symptoms was generally within the first five days after vaccination (Figure 4).

Figure 4. Time between vaccination and first symptoms, up to 14 October 2021



Source: Medsafe. 2021. *Adverse events following immunisation with COVID-19 vaccines: Safety Report #33 – 16 October 2021*. URL: https://www.medsafe.govt.nz/COVID-19/safety-report-33.asp.

There have been two reports of likely vaccine-mediated myocarditis with a fatal outcome. The coroner is investigating these reports. See Section 3.2 for further details about these reports.

2.3 Menstrual bleeding or unexpected vaginal bleeding

In June 2021, the Board considered menstrual disorders or unexpected vaginal bleeding as a potential safety signal for the Pfizer/BioNTech vaccine. At this time, CARM had received 22 reports of menstrual disorders or unexpected vaginal bleeding. The Board considered that the available evidence does not suggest an increased risk of these disorders following vaccination with the Pfizer/BioNTech vaccine. Medsafe will continue to monitor reports of menstrual disorders and unexpected vaginal bleeding.

Due to public interest and an increase in the number of reported cases (503 reports of menstrual disorders or unexpected vaginal bleeding up to 7 October 2021), this topic was brought back to the Board in October 2021 for review. The Board concluded that there was insufficient information to confirm a safety signal for menstrual disorders or unexpected vaginal bleeding with the Pfizer/BioNTech vaccine. Pfizer had also recently performed an in-depth analysis of heavy menstrual bleeding and postmenopausal bleeding and did not find a signal.

The Board recommended a communication from Medsafe on this topic to highlight that these disorders are common and can have many causes; and that any changes after COVID-19 vaccination are likely to be temporary, with no evidence that these temporary changes will impact future fertility. Medsafe published a Monitoring communication on 17 November 2021.

2.4 Use of the Pfizer/BioNTech vaccine in pregnancy

In May 2021 the COVID-19 Vaccine Technical Advisory Group (CV-TAG) recommended that pregnant people should be routinely offered COVID-19 vaccination at any stage of pregnancy.

There is a high level of public interest for the use of the COVID-19 vaccines in pregnancy, along with misinformation around this topic and the vaccine's effect on fertility. Therefore, it was important that the Board review the available information for use of the Pfizer/BioNTech vaccine in pregnancy, specific to the New Zealand context.

Medsafe presented the available data to the Board on 27 October 2021. The Board noted that there did not appear to be any concerns from the reported events to date for the use of the Pfizer/BioNTech in pregnant women. The Board also noted that pregnant women with symptomatic COVID-19 infection appear to have an increased risk of a more severe outcome (eg, ICU admission) in comparison with non-pregnant women of reproductive age and may also be at increased risk of preterm birth.

Medsafe will continue to closely monitor the use of the Pfizer/BioNTech vaccine in pregnancy through routine pharmacovigilance activities. The Board recommended that the CVIP send a communication to vaccinators around the risk/benefit considerations for the use of the Pfizer-BioNTech vaccine in pregnancy. Medsafe also published a Monitoring communication on 17 November 2021, stating that there are no safety concerns for the use of the Pfizer/BioNTech vaccine in pregnancy.

2.5 AEFIs in the elderly

In May 2020 a Norwegian study investigated reports of death in frail and elderly individuals residing in care home facilities after receiving the Pfizer/BioNTech vaccine. The review concluded that a causal link between the Pfizer/BioNTech vaccine and death was considered "likely" in 10 of the 100 cases, "possible" in 26 cases, and "unlikely" in 59 cases. The remaining five were deemed "unclassifiable." While emphasising considerable uncertainty around its conclusions, the authors acknowledged that adverse reactions from the vaccine in very frail elderly patients could initiate a cascade of complications, which in the worst-case scenario could lead to earlier death.

Based on this study, Medsafe conducted a review of the New Zealand data on AEFIs in the elderly to understand if these differed from other age groups, both in terms of the type of AEFIs reported and the severity. Medsafe presented a summary of the data to the Board on 21 July 2021. The Board concluded there was insufficient evidence to suggest that the vaccine had a disproportionate negative impact in the elderly compared to other age groups. However, the Board recommended an update to the data sheet around consideration of the risk/benefit profile for this age group, as below.

The data for use in the frail elderly (>85 years) is limited. The potential benefits of vaccination versus the potential risk and clinical impact of even relatively mild systemic adverse events in the frail elderly should be carefully assessed on a case-by-case basis.

3 Ad-hoc meetings

In addition to regular meetings every 3 to 4 weeks, the Board has the provision to hold ad-hoc meetings to discuss any urgent safety concerns that arise. An ad-hoc meeting of the Board would be triggered in the following circumstances:

- An urgent issue arising internationally that could threaten the stability of the CVIP
- A report of a serious unexpected event where further expert advice is urgently required by CARM, Medsafe or the CVIP.

The Board has held three ad-hoc meetings. The first was to discuss the concern developing overseas in relation to reports of thrombosis with thrombocytopenia syndrome (TTS) with the Janssen and AstraZeneca vaccines. The other two meetings have been following reports of potential vaccine-mediated myocarditis that resulted in death.

3.1 Thrombosis with thrombocytopenia syndrome safety concern

An ad-hoc meeting to discuss TTS was held on 22 April 2021. The purpose of the meeting was to discuss:

- if a similar risk has been identified in New Zealand
- whether the Pfizer/BioNTech vaccine is associated with this concern
- if it would be beneficial to provide information on this clotting/bleeding syndrome for the public, and if so, what communication would be needed.

At the time, a haematologist was not appointed to the Board and so Dr Laura Young was engaged to provide expert advice in this capacity. Dr Young was formally appointed as a Board member in August 2021, following an increase in the number of thrombotic and bleeding events reported for the Pfizer/BioNTech vaccine and the potential for New Zealand to start using the Janssen or AstraZeneca COVID-19 vaccines.

The Board considered the available information for TTS and was reassured by the extensive international experience with the Pfizer/BioNTech vaccine and the local experience to date in New Zealand. No risk was identified with the Pfizer/BioNTech vaccine. The Board recommended a Monitoring communication to reassure people that Medsafe is aware of the association between TTS and the Janssen and AstraZeneca COVID-19 vaccines, and that the safety of the Pfizer/BioNTech vaccine is being monitored closely for this issue but no such link has been identified.

3.2 Vaccine-mediated myocarditis death

The Board held an ad-hoc meeting on 9 August 2021 to discuss a fatal report of concern in an individual following COVID-19 vaccination.

On 2 August 2021, CARM received a report from a forensic pathologist for a woman who had passed away approximately four days after their first dose of the Pfizer/BioNTech vaccine. Myocarditis was a finding of the post-mortem examination that had not been recognised prior, with follow-up investigations indicating that the myocarditis could have been temporally associated with the individual's vaccination event.

At the 9 August 2021 meeting, the Director of CARM provided an overview of the case followed by a presentation from the forensic pathologist of their findings to date. The Board had also received an expert opinion from Dr Ralph Stewart, a cardiologist recently appointed to the Board.

The Board considered the potential causes of the individual's myocarditis, including the Pfizer/BioNTech vaccine, and noted the following.

- The Pfizer/BioNTech vaccine and some other COVID-19 vaccines increase the risk of myocarditis; Medsafe issued an Alert communication on 21 July 2021.
- COVID-19 infection increases the risk of myocarditis substantially more than COVID-19 vaccination.
- There are many possible causes of myocarditis, the most common being viral infection. Over 100 people are discharged from hospital with a principal diagnosis of myocarditis in New Zealand every year.
- In this case, other factors have been identified that may have potentially caused the myocarditis or led to a more severe myocarditis.
- The individual had no symptoms prior to the vaccine and the symptoms of myocarditis developed in the days immediately following the first vaccine dose.

The Board concluded that based on the currently available information, the vaccination event was the likely cause of the myocarditis. The Board considered that the circumstances of this case do not impact or change the known information on myocarditis, and the benefits of vaccination with the Pfizer/BioNTech vaccine for COVID-19 continue to greatly outweigh the risks of this rare side effect.

The forensic pathologist sent histology slides to cardiac pathologists in the United Kingdom (UK) and United States (US) for review to confirm the myocarditis type. Feedback received from the UK cardiac pathologist agreed with the findings of the case. Review from the US was still pending at the time the Board issued their statement; however, it was considered that this would not change the viewpoint taken by the Board.

The Board recommended that the Ministry of Health advise clinicians to be aware of myocarditis and pericarditis symptoms. The Ministry of Health issued a media release on 30 August 2021.

3.3 Potential vaccine-mediated myocarditis deaths

The Board met on 8 December 2021 to discuss three fatal reports of concern in individuals following COVID-19 vaccination.

In the week commencing 29 November 2021, CARM received three fatal reports for individuals who passed away in the period following vaccination, where vaccine-mediated myocarditis was proposed as the cause of death.

Two of the reported cases are under investigation by the coroner and were reported to CARM by the pathologists. The third case was reported to CARM by the district health board (DHB), following a review by their Adverse Reactions Committee.

High level details of the cases are presented below.

- A young adult man who passed away 12 days after their first dose of the vaccine. The Board understands he experienced symptoms that could be indicative of myocarditis in the days preceding his death.
- A young person who passed away 11 days after their second dose of the vaccine.
- A man in his 60s who passed away approximately one month after the second dose of the vaccine. The individual's death was not considered to be linked to the vaccine. However, following a review by the DHB, the death was reported due to the temporality of the vaccination event.

At the 8 December meeting, the Director of CARM provided an overview of the cases to the Board. The pathologist investigating the case of the young adult man and the forensic pathologist investigating the case of the young person both attended the meeting and presented their findings to date.

The death of the young person was discussed at length, however the Board considered that further information from pending investigations was needed before a determination on the role of the Pfizer/BioNTech vaccine could be made. A further ad-hoc meeting to discuss this case will be held once this information becomes available.

On review of the case of the man in his 60s, the Board considered the myocarditis was unlikely related to the vaccination event. The time from vaccination to the onset of symptoms and clinical factors point to other causes and is not consistent with a causal link.

The Board considered the death of the young adult man and noted the symptoms of myocarditis developed in the days following the first dose.

Based on the available information, the Board concluded that the vaccination event was the likely cause of the myocarditis in the young adult man.

The Board made the following recommendations to the CVIP around communications.

- Updating communications to the public on symptoms of potential myocarditis and pericarditis (eg, is chest pain sufficient or is this better reflected as chest pain, tightness and/or chest discomfort?).
- Ensuring that information on side effects is detailed at the time of vaccination; individuals need to be provided with verbal and written information about what to expect after their COVID-19 vaccine. This should include discussion of common and rare side effects and when/where/how an individual can seek medical advice.
- An update to the healthcare sector, in particular vaccinators, Whakarongorau, general practitioners and emergency departments, about the risk of myocarditis with the Pfizer/BioNTech vaccine and myocarditis signs/symptoms.

Myocarditis is a treatable condition, if identified, and outcomes are better the earlier that treatment is started. The Board considered that the circumstances of these cases did not impact or change the known information on myocarditis, and the benefits of vaccination with the Pfizer/BioNTech vaccine for COVID-19 continue to greatly outweigh the risks of this rare side effect.

The Board also noted that Medsafe was actively engaging with other international regulators to understand whether they have received similar reports.

On 20 December 2021, the Board issued a statement outlining the findings of the 8 December meeting.

4 CV-ISMB working group

The Ministry allocated resources to create a monitoring tool that allows for near real-time investigation of AESIs following immunisation. The monitoring tool compares cases observed at a particular point in time to what would be expected based on background rates. The CV-ISMB working group was set up to refine the logic used in these analyses and to provide guidance on any follow-up safety signal investigations. Based on the advice of the working group, the hospital discharge records were further interrogated to do specific signal investigations based on international concerns.

4.1 Members

The CV-ISMB working group consists of volunteers from the Board and a representative from Medsafe (Table 2).

Table 2: CV-ISMB working group members and expertise

Name	Expertise
Honorary Associate Professor Hilary Longhurst (ISMB Deputy Chair)	Clinical immunologist
Associate Professor Matt Doogue	Clinical pharmacologist
Professor Thomas Lumley	Biostatistics
Honorary Professor Ralph Stewart	Cardiologist
Dr Enver Yousuf	General medicine and pharmaceutical medicine
Dr Susan Kenyon (Manager Clinical Risk, Medsafe)	Medsafe representative

4.2 Observed vs expected analysis (rapid cycle analysis)

Rapid Cycle Analysis (RCA) allows for near real time detection of AESIs by calculating the relative risk (RR) at a specific point in time from observed and expected rates within specific risk windows. To do this effectively, criteria used to measure these AESIs must be individualised. For example, the onset time of a particular disease could influence the risk window, or a subset of the population might be at higher risk. The CV-ISMB working group has agreed to help refine the criteria used to detect a select amount of AESIs for COVID-19 vaccines. The Board provided further feedback on publishing mortality rates following vaccination with the Pfizer/BioNTech vaccine in Medsafe's COVID-19 Vaccine Safety Report #36.

4.3 Specific safety questions

Based on reports of vaccine-mediated myocarditis, the CV-ISMB working group requested further interrogation of the hospital discharge records to investigate whether people with a pre-existing heart condition were at a higher risk of death following immunisation. The working group was engaged to provide further insight and technical expertise to approach this problem.

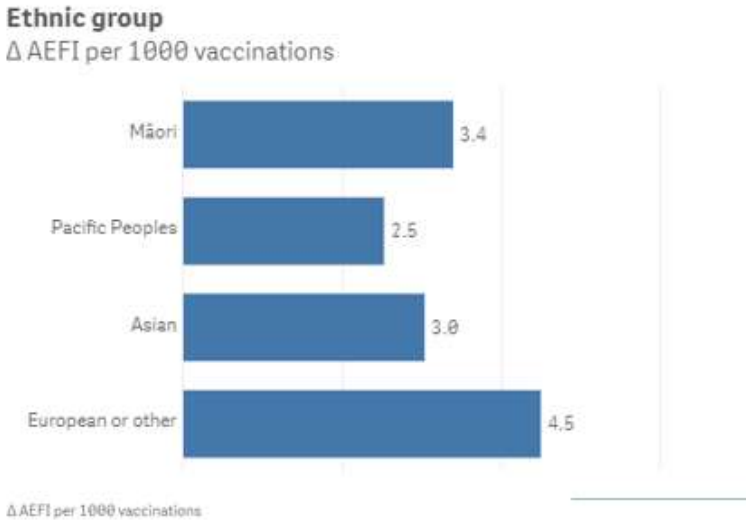
Several approaches were used to assess the risk following vaccination with the Pfizer/BioNTech vaccine. The preliminary data suggests that people with a pre-existing heart condition are not at increased risk of mortality following vaccination.

5 Under-reporting of AEFIs

Vaccine uptake significantly increased through August and early September 2021. On 15 September 2021, Medsafe provided an overview of reported adverse events by ethnicity to the Board.

Underreporting for Pacific Peoples was noted, with a reporting rate of 0.25%, while the reporting rates for Māori (0.34%) and Asian (0.3%) were also lower than the overall reporting rate (see Figure 5). There was no clear difference in the types of AEFI reported by ethnicity. However, a lack of engagement with consumer reporting for Pacific Peoples was evident, based on the significantly lower proportion of consumer reports for Pacific Peoples (16.7%) compared to all groups combined (31.0%) (see Figure 6 and Figure 7; consumer reports are labelled as Public:Patient).

Figure 5. Reporting rate by ethnic group, up to 14 September 2021



Source: Ministry of Health Qlik app.

Figure 6. Overall reporter type, up to 14 September 2021

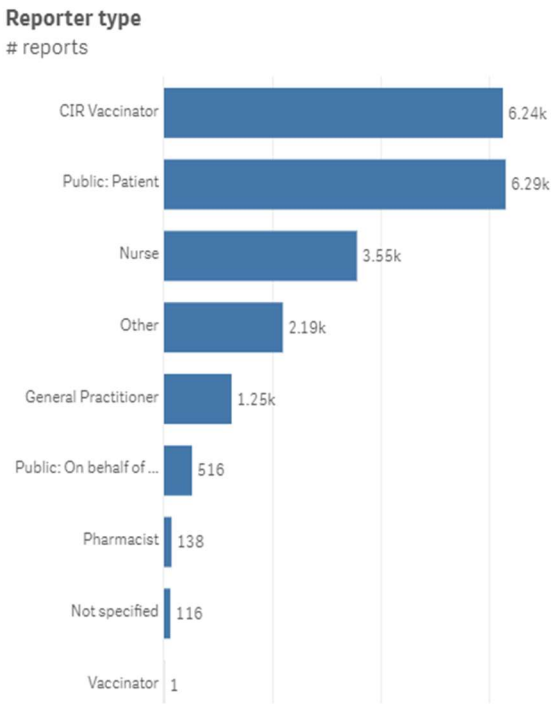
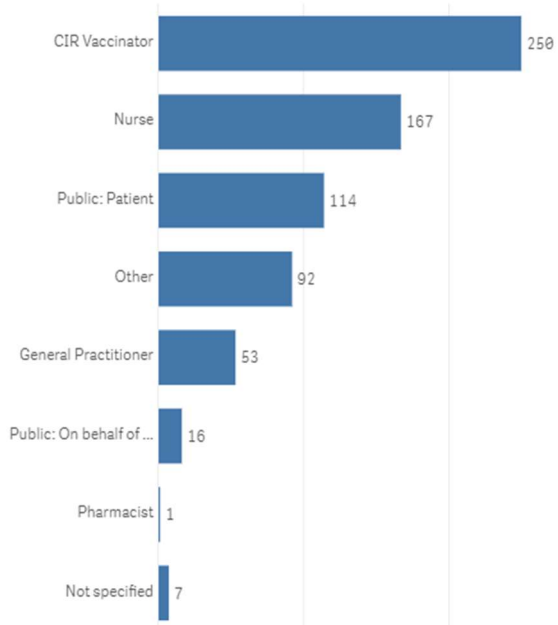


Figure 7. Pacific Peoples* reporter type, up to 14 September 2021



* Refers to the ethnicity of the patient, not the reporter.

Source: Ministry of Health Qlik app.

The Board recommended communicating to the public around underreporting of AEFIs in Pacific Peoples, along with guidance around the AEFI reporting process. If reporting is emphasised for Pacific Peoples, this would likely have a positive impact on reporting rates across in ethnicities. Consideration should also be given to translation of any communication, to enable better access to information.

The National Director, CVIP agreed to this recommendation, and it is being actively worked on in the Programme by Post Event, Equity, and Communications. Ideas being explored include:

- increased messaging at vaccination sites around the 'why' for adverse event reporting
- capturing AEFIs through alternative approaches other than consumers completing the CARM webform (eg, healthcare professionals and vaccinators reporting on behalf of consumer)
- general communications targeted to consumers and healthcare professionals explaining the importance of reporting for COVID-19 vaccines and how to make a report.

6 ISMB support to Pacific countries

6.1 Participating countries

The Realm countries (Cook Islands, Niue and Tokelau) have used Pfizer/BioNTech vaccine doses donated by New Zealand for their respective vaccine rollouts. Vaccinations commenced on 18 May 2021 in the Cook Islands for their 16+ year-old population, with Niue and Tokelau following two months later. The requirement from Pfizer for donating the vaccine to these countries was dependent on the New Zealand Ministry of Health providing adequate pharmacovigilance support. This included receiving, documenting, anonymising, and assessing all AEFIs, and reporting these back to Pfizer.

Conversely, Samoa, Tonga and Fiji had received other vaccines for their general populations and received support from New Zealand related to training, cold storage and consumables. These countries later received donations of the Pfizer/BioNTech vaccine for their younger population (ranging from 12 to 17 years, see Table 3). These countries already had adequate pharmacovigilance capabilities, and only required support with reporting AEFIs back to Pfizer and accessing medical advice for treatment and management of serious AEFIs. A secure Microsoft Teams channel has been created to facilitate direct reporting of AEFIs to Pfizer, and the Immunisation Advisory Centre (IMAC) medical advisors are providing medical advice to Samoa, Tonga and Fiji as needed.

6.2 Role of the CV-ISMB

The Director-General of Health (DG) established the Board for the purposes of providing technical advice on the safety of COVID-19 vaccines during the rollout across Aotearoa New Zealand. The Board also provides support to the Pacific countries that were offered access to Aotearoa New Zealand's vaccine portfolio. The Board's expertise, specifically their knowledge around adverse events following the Pfizer/BioNTech vaccine, is invaluable for a successful vaccine rollout in these countries.

The Board's support was crucial for the three Realm countries, because these countries have limited domestic capacity and capability to meet the Pfizer pharmacovigilance system requirements for vaccine dose donation. Support was also extended to Samoa, Tonga, and Fiji, even though their pharmacovigilance systems were more advanced.

Table 3 provides a summary of the vaccine rollout in these countries, and AEFI reporting to date.

Table 3. Countries receiving CV-ISMB support, and summary of the Pfizer/BioNTech vaccines donated, data to 21 December 2021

Country	Date vaccine rollout started (Pfizer only)	Doses administered	Population receiving Pfizer (years)	AEFIs	CV-ISMB advice requested
Cook Islands[a]	18 May 2021	23,049	12+	91	None
Niue[a]	10 Jun 2021	2,352	12+	8	None
Tokelau[a]	19 Jul 2021	1,936	12+	21	None
Samoa[a,b]	25 Oct 2021	41,669	12–17	15	None
Tonga[a,b]	22 Oct 2021	24,375	12–17	31	None
Fiji[b]	15 Nov 2021	25,049	12–14	0	None

a. Includes pregnant women who are eligible
b. Samoa, Tonga and Fiji used different vaccines for their adult populations.

7 AstraZeneca COVID-19 vaccine use in New Zealand

Medsafe provisionally approved the AstraZeneca COVID-19 vaccine on 22 July 2021. In October/November 2021, the Programme recognised that a second vaccine was needed for people who:

- had experienced a serious adverse event after their first dose of the Pfizer/BioNTech vaccine and were advised not receive the second dose of this vaccine
- preferred a different type of vaccine technology (viral vector rather than mRNA).

Following a recommendation by CV-TAG, Cabinet approved the use of the AstraZeneca vaccine in New Zealand. The vaccine became available for use on 29 November 2021.

Medsafe will bring an overview of the New Zealand safety data for the AstraZeneca vaccine to the Board in late January 2022.

8 Conclusion

In 2021, the CV-ISMB has held 16 meetings (including three ad-hoc meetings) to review and discuss safety data for the COVID-19 vaccines.

The data cut-off for this report is 28 November 2021, at which point only the Pfizer/BioNTech vaccine was available in New Zealand. More than 7 million doses of the Pfizer/BioNTech vaccine had been administered and almost 90 percent of the eligible population (12 years and older) had received two doses of the Pfizer/BioNTech vaccine. The Programme also recommended a third dose for immunocompromised (primary course) people and Medsafe approved a booster dose for adults.

The Board has considered 18 safety signals for the Pfizer/BioNTech vaccine, which has led to 28 recommendations to either Medsafe or the Programme. To date, only one safety signal has been confirmed, with myocarditis and pericarditis identified as very rare adverse reactions to the Pfizer/BioNTech vaccine. Information about myocarditis and pericarditis was added to the vaccine data sheet in July 2021.

Sadly, there have been two deaths likely associated with the Pfizer/BioNTech vaccine. The coroner is still investigating, but vaccine-mediated myocarditis was implicated as the cause of death in both cases. Following review of both cases, the Board issued statements in August and December 2021 advising the public and healthcare professionals to be aware of the signs and symptoms of myocarditis. Based on the information presented for the second case in December 2021, the Board also made recommendations to the Programme around the importance of communications for myocarditis.

The Board continues to closely monitor myocarditis cases reported in New Zealand along with the international evidence. The Board considers that the benefits of vaccination with the Pfizer/BioNTech vaccine continue to greatly outweigh the risks of this rare adverse reaction. In early 2022, Medsafe along with the Programme will commence a study to follow up reported cases of myocarditis and pericarditis in New Zealand, which will further enhance our understanding of this adverse reaction and its impact.

Other safety signals reviewed throughout 2021 for the Pfizer/BioNTech vaccine have included anaphylaxis, thrombosis, stroke, menstrual disorder, herpes zoster and tinnitus. For all of the safety signals, the Board recommended that Medsafe should continue monitoring these respective events through routine pharmacovigilance activities. The Board also reviewed the available safety data around the use of the Pfizer/BioNTech in pregnancy, with no concerns identified. Vaccine use in pregnancy will continue to be a key focus for the Board, Medsafe and the Programme as this data continues to mature in 2022. The Board continues to closely monitor the safety data of the Pfizer/BioNTech vaccine in children. Available data for children aged 12 years and older was reviewed in September and December 2021 and no concerns were identified. Vaccine use in children will be another key focus area for 2022.

Given the large proportion of the population being vaccinated in a relatively short period of time, there is an expected background level of adverse events occurring in close temporality to

the vaccination event. However, the Board has been reassured by both the international and New Zealand data presented, that the Pfizer/BioNTech vaccine is a very safe vaccine.

Looking ahead to 2022 will see safety data available for the AstraZeneca COVID-19 vaccine, along with the administration of booster doses for most of the population, 18 years and older and the rollout of the Pfizer/BioNTech vaccine in younger children (aged 5–11 years).

Appendix 1

Terms of Reference of the COVID-19 Vaccine Independent Safety Monitoring Board

1. Introduction

Given the desire to clearly indicate the independence of this group from the rest of the COVID-19 Vaccine & Immunisation Programme (CVIP), Medsafe and the Ministry of Health, the group is to be named the COVID-19 Vaccine Independent Safety Monitoring Board.

These Terms of Reference establish the Independent Safety Monitoring Board (the Board) to support the COVID-19 Vaccine and Immunisation Programme and set out the:

- role and functions of the Board
- composition of the Board
- term and workplan requirements
- reporting requirements
- terms and conditions of appointment
- duties and responsibilities of Board members.

2. Functions of the Board

The purpose and function of the Board is to provide expert advice on the safety of COVID-19 vaccine(s) during the rollout across Aotearoa New Zealand and in support of Fiji and the six Polynesian countries: the three Realm countries (Cook Islands, Niue, Tokelau) and Samoa, Tonga and Tuvalu offered access to Aotearoa New Zealand's vaccine portfolio. The Board does not have powers of veto, direction, or instruction actual or implied.

The Board is to be a pool of experts convened to:

- assess potential causal links between adverse events following immunisation (AEFI) and adverse events of special interest (AESI) and COVID-19 vaccines;
- review all serious or significant AEFIs presented for expert opinion;
- provide expert advice to Medsafe, the CVIP, Ministry of Health and if requested the Health Authorities within the six Polynesian countries and Fiji in relation to the balance of benefits and risks (ie, safety or efficacy) of COVID-19 vaccines;
- consider information about the safety of COVID-19 vaccines that is referred to the Board by the Centre for Adverse Reactions Monitoring (CARM) and/or Medsafe and provide expert advice to Medsafe, the CVIP, Ministry of Health and, if requested, the Health Authorities within the six Polynesian countries and Fiji, on:
  - the interpretation of the information
  - the significance of the information in relation to the risk-benefit profile of the vaccine
  - whether an issue needs referral to the Medicines Adverse Reactions Committee (MARC) for advice or Medsafe should consider regulatory intervention
  - if a potential hold or stop to the CVIP is required

- confirming CVIP process and procedures;
- ensure that equity is a key consideration in the collection, monitoring and reporting of AEFI to uphold the Crown's commitment to Te Tiriti o Waitangi and achieving equitable health outcomes for all people in Aotearoa New Zealand.

The ultimate decision(s) about regulatory intervention and the programme rollout within Aotearoa New Zealand will be made by Medsafe and the Ministry of Health respectively. The six Polynesian countries and Fiji will have their own government processes regarding their COVID-19 vaccination programmes.

3. Composition of the Board

The Chair and other members of the Board are drawn from experts in various fields of clinical medicine, microbiology, epidemiology and biostatistics.

The Board also holds a position for a lay person (non-healthcare professional) to represent consumer interests.

The term of membership will be determined by the CVIP. In making themselves available for appointment, members should ensure that:

- there is no conflict of interest which would preclude their appointment; and
- they are available to serve for the full term of their appointment.

Co-opted non-voting members
Not limited to the Director of the New Zealand Pharmacovigilance Centre (NZPhvC), a representative from the Immunisation Advisory Centre (IMAC), technical experts from Medsafe, the CVIP and from within the Ministry and representatives from Fiji and the six Polynesian countries can also have membership of the Board as needed.

Ex-Officio (non-voting)
Chairperson of COVID-19 Vaccine Technical Advisory Group.

4. Workplan development

The Board will not be asked to develop a work plan. Information will be presented to the Board for consideration and advice by CARM, Medsafe, the CVIP and the Ministry.

5. Reporting Requirements

The Board will make recommendations to the COVID-19 Vaccine and Immunisation Programme (CVIP) Steering Group, copied to Medsafe. Recommendations may also be made directly to Global Health, Ministry of Health regarding the six Polynesian countries and Fiji. Medsafe, the CVIP Steering Group and Global Health can discuss findings with the Chair of the Board.

When ad hoc meetings of the Board are held, summaries will be produced by the secretariat but not published. Summaries are subject to the Official Information Act 1982 (OIA), but any confidential information will be withheld.

The Chair of the Board will not be a direct media contact but will be available for public comment at the request and arrangement of the Ministry.

A report to the CVIP Steering Group and Medsafe will be provided at the Board's end date.

6. Establishment, Review process and End Date

The Board will be established by the Director General for the purposes of providing technical advice on the safety of COVID-19 vaccines during the rollout across Aotearoa New Zealand and in support of Fiji and the six Polynesian countries: the three Realm countries (Cook Islands, Niue, Tokelau) and Samoa, Tonga and Tuvalu offered access to Aotearoa New Zealand's vaccine portfolio.

The Board's Terms of Reference will be reviewed at 12 monthly intervals alongside the Ministry's annual stocktake of Ministerial and Ministry Groups.

7. Meetings

It is intended that the Board will do most of its work virtually via email and teleconferencing. If necessary, meetings will be held on an ad hoc basis. Meetings may be held face-to-face if necessary and appropriate. There may be a preliminary face to face meeting of the Board (COVID alert levels permitting) to consider data requirements and to be provided with an overview of the CVIP and strategy.

The Board will determine its own meeting frequency around the key milestones which may include but not limited to sequencing, change points and data report publications. The Board will be on call for any serious or significant adverse events during the rollout.

There may be, at the discretion of the chair, both open and closed sessions for the Board, the sequence of which will be determined by the Board. Open sessions will enable the attendance of co-opted non-voting members.

At any meeting of the Board most of the appointed members must be present to form a quorum (the ISMB membership is established at 14 members, so eight members form a quorum). All members forming the quorum must be eligible to vote, for example not abstaining from discussion due to a conflict of interest.

The dossier will be transmitted and accessed via a secure electronic file transfer system (EFT) made available to members where practical at least one week before each meeting to allow time for preparation. Information on urgent medicine safety issues will be sent to members where practical two days prior to the meeting.

The Secretariat of the Board is provided by the CVIP. The Secretariat will:

- process travel and expense claims
- process preparation and attendance fees
- prepare the agenda and dossier for each meeting
- prepare the minutes of each meeting
- report back to the Committee on action(s) taken since the previous meeting.

8. Duties and Responsibilities of a Member

Members have a commitment to work for the public of Aotearoa New Zealand. Members are accountable to the Ministry of Health. Board members ensure familiarity with and provide advice that is congruent with the principles of Te Tiriti o Waitangi to prioritise equitable health outcomes for Māori.

Board members attend meetings and undertake Board activities as independent persons responsible to the Board as a whole and are not representatives of professional organisations or communities. This issue is particularly important when Board members may, at times, be required to be party to decisions which conflict with the views of other organisations with which they are involved.

There is an expectation that members will attend all meetings and devote sufficient time to become familiar with the affairs of the Board and the wider environment within which it operates.

Members of the Board are asked to:

- ensure all activity and advice is undertaken with consideration of and respect for equity of outcomes across all people in Aotearoa New Zealand, including but not limited to; ethnicity, disability, geographic location, age, health, gender and socioeconomic position, living and working conditions;
- provide guidance for AEFI investigations so that the cause can be determined correctly;
- assess potential causal links between AEFIs and vaccines, using standard procedures;
- develop standard protocols for management of review of adverse events (ie, serious allergic reactions);
- members may nominate additional expertise if required, but these must be agreed by the chair and Ministry;
- provide guidance on potential signals of previously unrecognized vaccine-related adverse events and support further investigations to establish if causality exists;
- make recommendations to action any issues which may arise, communicate with national stakeholders and other national and international experts, when required.

9. Removal from the Board

The Ministry may, at any time and entirely at the Ministry's discretion, remove any member from the Board.

The Ministry may, at any time, exclude a member from discussions of the Board in the case of a conflict of interest.

10. Conflicts of Interest

Members should perform their functions in good faith, honestly and impartially and avoid situations that might compromise their integrity or otherwise lead to conflicts of interest. Proper observation of these principles will enable public confidence in the work of the Board to be maintained.

When members believe they have a conflict of interest on a subject which will prevent them from reaching an impartial decision or undertaking an activity consistent with the Board's functions, then they must declare a conflict of interest and absent themselves from the discussion and/or activity. This must be done at the earliest possible opportunity, in the regular agenda item around conflicts of interest, and at the point the relevant item of business comes up in the meeting.

The European Medicines Agency (EMA) policy on the handling of competing interests of scientific committees' members and experts will be used to determine conflicts of interest and participation in meetings.

11. Liability

Members are not liable for any act or omission done or omitted in their capacity as a member, if they acted in good faith, and with reasonable care, in pursuance of the functions of the Board.

12. Confidentiality

Meetings, including agenda material and minutes, are confidential. Members must ensure that the confidentiality of Board business is maintained.

Members are free to, and are expected to, express their own views within the context of meetings, or the general business of the Board. Members must publicly support a course of action decided by the Board, or if unable to do that, must not publicly comment on decisions.

At no time shall members divulge details of Board matters or decisions to people who are not members, or Ministry employees. Disclosure of Board business to anyone outside the Ministry must be the decision of the Ministry.

Board members must ensure that documents are kept securely to ensure that confidentiality is maintained. Release of correspondence or papers can only be made with the approval of the Ministry. At the end of a member's term, all Board information must be returned to the Ministry.

13. Remuneration and expenses

Members of the Board are paid fees for attendance at meetings, in accordance with the Cabinet Office Circular CO (12) 6 *Fees framework for members appointed to bodies in which the Crown has an interest* (or its successor circular).

The fee for Board members is currently $865 per day and $108 per hour for any part day (before tax) and this is reviewed annually.

Members who are employees of the wider State sector are not entitled to be paid fees for Board business if this is conducted during regular paid work time (ie, members cannot be paid twice by the Crown for the same hours).

Members are entitled to be reimbursed for actual and reasonable travelling and other expenses incurred in carrying out their duties. The expectation is that the standards of travel, accommodation, meals and other expenses are modest and appropriate to reflect public sector norms.

Appendix 2

Anaphylaxis Checklist for: Vaccinator

STEP 1. Record Patient Details:

Patient Name	*NHI*	*CIR Adverse Event Code*	*Patient Phone No.*

Adrenaline Given Time	*Adrenaline Dose*	*Transfer to ED (Name)*	*Transfer Time*

STEP 2. Record course of illness:

Must be able to check both 2.1 and 2.2 to meet any level of certainty for anaphylaxis.

☐ **2.1 SUDDEN ONSET of signs & symptoms**

AND

☐ **2.2 RAPID PROGRESSION of signs & symptoms**

"An event that occurred unexpectedly and without warning leading to a marked change in a subject's previously stable condition"

STEP 3. Tick Symptoms and Signs:

Check all symptoms/signs present by ticking appropriate boxes in rows below.
Anaphylaxis requires two or more body systems involved.

Body System	B. Major Criteria	C. Minor Criteria	
Skin **Excluding hereditary angioedema*	☐ Generalized urticaria (hives) ☐ Generalized erythema ☐ Angioedema* (general or localized including lip) ☐ Generalized pruritus WITH skin rash	☐ Localized injection site urticaria ☐ Red AND itchy eyes ☐ Generalized prickle sensation ☐ Generalized pruritus WITHOUT skin rash	
Respiratory	☐ Bilateral wheeze (bronchospasm; by stethoscope) ☐ Stridor ☐ Upper airway swelling (tongue, throat, uvula, larynx) ☐ ≥ 2 indicators of respiratory distress: ☐ Tachypnea ☐ Cyanosis ☐ Grunting ☐ Chest wall retractions ☐ Increased use of accessory respiratory muscles	☐ Persistent dry cough ☐ Hoarse voice ☐ Sensation of throat closure ☐ Sneezing OR rhinorrhea ☐ Difficulty breathing WITHOUT wheeze or stridor	
Cardiovascular (CVS)	☐ Measured hypotension ☐ ≥ 3 signs of uncompensated shock: ☐ Tachycardia ☐ Capillary refill >3 seconds ☐ Reduced central pulse volume ☐ Decreased level or loss of consciousness	☐ ≥ 2 signs of reduced peripheral circulation ☐ Tachycardia ☐ Capillary refill >3 seconds ☐ Decreased level of consciousness	
Gastro-intestinal (GI)	None	☐ Nausea ☐ Abdominal pain	☐ Vomiting ☐ Diarrhea
Laboratory	None	☐ Elevated mast cell tryptase (> upper normal limit for laboratory doing test)	

STEP 4. Upload this form to the Centre for Adverse Reactions Monitoring (CARM) Dropbox:
https://www.dropbox.com/request/tvmefV4XPpGdKfAyr07L

GLOSSARY OF TERMS

Accessory muscles	Muscles, primarily in the neck (sternocleidomastoid which elevates sternum; scalene group which elevates upper ribs) which assist but don't play a primary role in breathing. When used at rest they indicate a level of respiratory distress or increased work of breathing.
Angioedema	Areas of deeper swelling of the skin and/or mucosal tissues in either single or multiple sites which may not be well circumscribed and usually not itchy. (Reported symptoms of "swelling of the tongue" or "throat swelling" should not be documented as angioedema unless there is visible skin or mucosal swelling). NOTE: hereditary angioedema, usually with a history of recurrent episodes of swelling, should be excluded (affects 1 in 50,000).
Capillary refill time	The time required for normal skin colour to reappear after a blanching pressure is applied for 5 seconds. Usually assessed by pressing on the nail bed to cause blanching and then counting the time it takes for the blood to return to the tissue indicated by a pink colour returning to the nail. It normally takes < 3 seconds.
Cyanosis	A dark bluish or purplish discolouration of the skin and/or mucous membranes due to lack of oxygen in the blood
Dry cough	Rapid expulsion of air from the lungs and not accompanied by expectoration/sputum (a non-productive cough)
Erythema	Abnormal redness of the skin without any raised skin lesions
Generalized	Involving >1 body site – that is each limb is counted separately as is the abdomen, back, head and neck
Grunting	A sudden and short noise with each breath when breathing out
Hoarse voice	An unnaturally harsh cry in an infant or vocalisation in and adult or child
Hypotension	An abnormally low blood pressure (BP) documented by appropriate measurement. For infants and children: age specific systolic BP <3-5th percentile OR >30% decrease from that person's baseline; For adults: Systolic BP of <90mm Hg or >30% decrease from that person's baseline.
In-drawing or retractions	Inward movement of the muscles between the ribs (inter-costal), in the lower part of the neck (supra-clavicular or tracheal tug) or below the chest (sub-costal). The movements are usually a sign of difficulty with breathing which results in increased use of 'accessory respiratory muscles' (sternocleidomastoid and intercostal).
Injection site urticaria	Urticaria which is continuous with the injection site or involves other aspects of the injected limb
Localised	Involving one body site only
Loss of consciousness	Total suspension of conscious relationship with the outside world as demonstrated by an inability to perceive and respond to verbal, visual or painful stimulus
Mast cell tryptase	Inflammatory mediator released by mast cells during acute anaphylaxis. Typically levels peak between 15 and 120 minutes after onset; samples for measurement should be taken within 6 hours of onset of signs/symptoms.
Prickle sensation	An unpleasant skin sensation that provokes the desire to run and/or scratch to obtain relief
Pruritus	Itchiness
Red and itchy eyes	Redness of the whites of the eyes (sclera) with sensation that provokes the desire to rub and/or scratch to obtain relief.
Retractions	Indrawing of skin while breathing in (implies an obstruction to breathing); may be supraclavicular (above the collarbone), suprasternal (above the sternum), intercostal (between the ribs), substernal (below the sternum) or subcostal (abdomen just below the rib cage)
Rhinorrhea	Discharge of thin nasal mucus
Sensation of throat closure	Feeling or perception of throat closing with a sensation of difficulty breathing
Sneezing	An involuntary (reflex), sudden, violent, and audible expulsion of air through the mouth and nose.
Stridor	A harsh and continuous sound made on breathing in
Tachycardia	Faster than normal heart rate which varies by age – Adult >100 bpm
Tachypnoea	Faster than normal respiratory rate which varies by age – Adult >16 bpm
Urticaria	Localized redness of superficial layers of skin that is itchy, raised, sharply demarcated and transient (that is skin changes at any location are usually present for less than 12 hours)
Wheezing	A whistling, squeaking, musical or puffing sound made on breathing out