Final report 2022

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

Published 3 July 2023

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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.

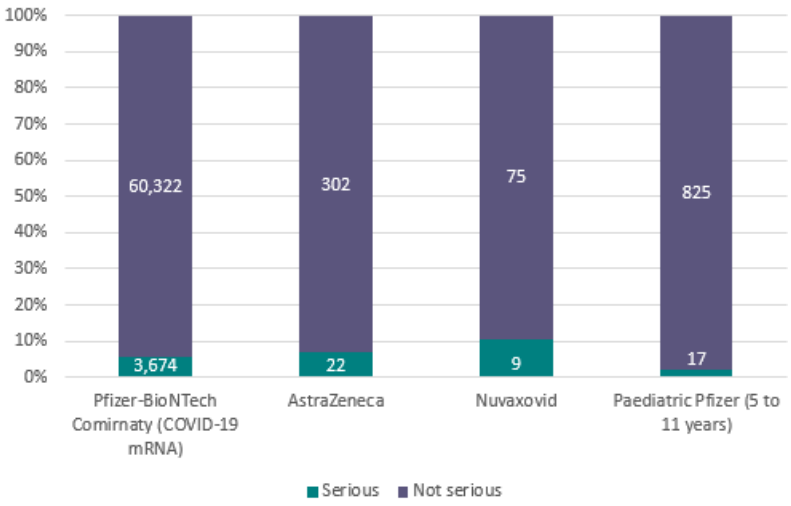
1 Overview

Cases investigated (up to 28 November 2022)

Number of AEFIs reported in the COVID CARM database: **63,999**
Number of Pfizer/BioNTech COVID-19 vaccine doses administered: **11,977,450**
Number of paediatric Pfizer/BioNTech COVID-19 vaccine doses administered: **425,544**
Number of AstraZeneca COVID-19 vaccine doses administered: **9,047**
Number of Novavax COVID-19 vaccine doses administered: **7,479**

Total number of serious cases reported to CARM	Serious cases presented to CV-ISMB	Safety signals investigated
3,676	**784**	**25**

Figure 1: AEFI reported by seriousness for the Pfizer/BioNTech, AstraZeneca, Novavax and paediatric Pfizer/BioNTech COVID-19 vaccines in New Zealand.



CV-ISMB meetings

Members recruited	17
Meetings held	28
Number of recommendations	40

NOTE: Given that more than 4 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 February 2021, New Zealand began its largest immunisation programme using the Pfizer/BioNTech COVID-19 (Comirnaty) mRNA vaccine, with the goal to vaccinate as many of the eligible population as possible against COVID-19. The rollout has continued into 2022 with the availability of alternative COVID-19 vaccines (AstraZeneca and Novavax), the addition of booster doses and introduction of the paediatric Pfizer/BioNTech COVID-19 vaccine for 5–11-year-olds.

The COVID-19 Vaccine Independent Safety Monitoring Board (CV-ISMB) was established in February 2021. The role 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 National Immunisation Programme, Te Whatu Ora and the Ministry of Health. In addition, the Board is available to provide support (if requested) to the 7 Pacific countries offered access to New Zealand's vaccine portfolio.

In April 2022, the Board released an interim report for 2021 (data cut off 28 November 2021) detailing their review and consideration of the safety data for the Pfizer/BioNTech COVID-19 vaccine in New Zealand. This report builds on the interim report, providing details of the Board's work throughout 2022.

The key focus areas for the Board in 2022 remained:

- supporting the 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 presented for expert opinion (this includes all fatal reports)
- advice to Medsafe and the Programme 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.

1.2 Members

The Chair and 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.

In 2022, the Board added a second paediatrician following the introduction of the paediatric Pfizer/BioNTech COVID-19 vaccine, taking the membership to 17.

1.2.1 Chair and Deputy Chair

Dr John Tait (Chair) *(MB, MS, FRCOG, FRANZCOG)*
Dr 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. Dr 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. Dr 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, MAvMedicine, PGDipOccMed, PGCertTravMed, PGCertHsC(Sports Med), FRNZCGP)*
Dr Heather is general practitioner (GP) working at Etu Pasifika Auckland Clinic. She also is a Senior Lecturer and researcher in Pacific Health at the University of Auckland and GP teacher and clinical lead for GP registrars training in clinic. She is involved in a number of boards and committees including a member of the Pacific Chapter RNZCGP, Pasifika Medical Association Membership Board Director, Pu Manawa Rheumatic fever/RHD Pacific Governance Board, Auckland executive faculty board RNZCGP, NZ Breast Foundation Medical Advisory Committee. Dr Heather brings a wealth of expertise in Primary Care, Pacific Health, and Equity.

Dr Tom Hills *(MBChB, MSc, DPhil, FRACP)*
Dr Hills is a University of Otago-trained Clinical Immunologist and Infectious Diseases Physician 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, infectious diseases, and clinical trials.

Dr Wendy Hunter *(MBChB, Dip Paeds, FRACP)*
Dr Hunter is a consultant general paediatrician working at Nelson Hospital. She is a Clinical Senior Lecturer at the Christchurch School of Medicine, University of Otago. She has also served as an intern supervisor and on several training committees at the Royal Australasian

College of Physicians (RACP). Dr Hunter provides expertise in paediatrics, along with a rural perspective.

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 6 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 Te Whatu Ora Waitemata and is acute lead in paediatrics. He is the current chair of the Immunisation Response Governance Group Northern (IRGGN) and the National immunisation Taskforce. Dr Sinclair lectures in Māori health at the University of Auckland and is the president elect lead of 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 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 fields of pharmacovigilance, 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).

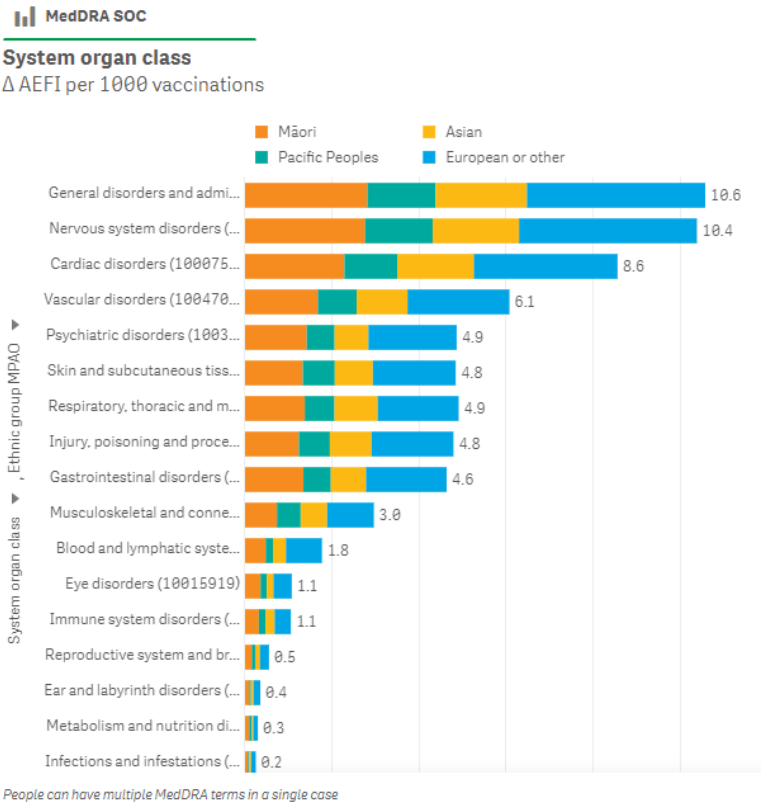
1.3 Equity

A 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 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.

Qlik applications are used for the visualisation of safety data for the COVID-19 vaccines. Standardisation of reported AEFI by ethnicity has not shown any differences for frequently reported AEFI or adverse events of special interest such as myocarditis and pericarditis.

Figure 2: Visualisation from Qlik app of reported AEFIs per 1,000 vaccinations by systemic organ class and ethnicity.



Source: Ministry of Health Qlik app.

Following an update from Medsafe in September 2021, the Board noted underreporting for Pacific peoples in New Zealand. Further information is provided in the Board's interim report for 2021. An update on the ongoing efforts to improve engagement of Pacific peoples with AEFI reporting was provided to the Board in March 2022. At this time the Programme was working closely with the Ministry of Health, Pacific Health and communications teams to produce simplified and accessible messaging around the who, what, when, where and how for AEFI reporting. The Board commented that this was potentially a system issue, however, it was good that efforts were being made to address some of these access issues.

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 (O/E) analysis if background rate data is available
- Safety Reports from 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
- a Monitoring communication from Medsafe
- an Alert communication from Medsafe
- updating the product information (data sheet and consumer medicine information)
- holding or stopping the immunisation programme.

Throughout 2021 and 2022, Medsafe evaluated 24 safety signals for the Pfizer/BioNTech COVID-19 vaccine. In addition, reviews have also been conducted for both the AstraZeneca and Novavax COVID-19 vaccines, with one safety signal investigated for the Novavax 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 or further information is obtained from other regulatory agencies and the sponsor.

Table 1 provides a summary of these investigations for the Pfizer/BioNTech COVID-19 vaccine, 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.

Information on reviews and investigations for the AstraZeneca and Novavax COVID-19 vaccines is detailed in section 4 and section 5 of this report, respectively.

Table 1. Summary of investigations into possible safety signals for the Pfizer/BioNTech vaccine

Safety signal (no. of times presented to board)	Outcome	Most recent time considered	Explanation	Regulator action
Thrombosis with thrombocytopenia syndrome (TTS) (1)	Unlikely association. Continue to monitor. See also the Monitoring communication.	22/04/21	The Board was reassured by the international experience with the Pfizer/BioNTech COVID-19 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 COVID-19 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 COVID-19 vaccine is being monitored closely for this issue.	Y
Appendicitis (1)	Unlikely association. Continue to monitor.	27/05/21	The Board agreed that current evidence does not suggest a side effect of 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	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	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	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 evidence 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	Explanation	Regulator action
Seizure (1)	Unlikely association. Continue to monitor.	21/07/21	The Board agreed that the current data does not suggest a side effect of seizures, and that Medsafe should continue monitoring through routine pharmacovigilance activities.	N
Glomerular diseases (1)	Unlikely association. Continue to monitor.	25/08/21	The Board agreed that the current evidence does not suggest a side effect of glomerular disease, and that Medsafe should continue monitoring through routine pharmacovigilance activities.	N
Menstrual disorder (2)	Unlikely association. Continue to monitor. See also the Monitoring communication.	27/10/21	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
Stroke (2)	Unlikely association. Continue to monitor.	17/11/21	The Board agreed that current evidence does not suggest a side effect of stroke, and that Medsafe should continue monitoring through routine pharmacovigilance activities.	N
Erythema multiforme (1)	Unlikely association. Continue to monitor.	17/11/21	The Board agreed that current evidence does not suggest a side effect of erythema multiforme, and that Medsafe should continue monitoring through routine pharmacovigilance activities.	N
AEFIs in children (12+ years) (2)	Unlikely association. Continue to monitor.	15/12/21	The Board agreed that the current data does not suggest a new safety concern for AEFIs in children (12+ years), and that Medsafe should continue monitoring through routine pharmacovigilance activities.	N
Myalgic Encephalomyelitis (ME)/Chronic Fatigue Syndrome (CFS) (1)	Unlikely association. Continue to monitor.	26/01/22	The Board were reassured by the data and recommended the continuation of routine pharmacovigilance to monitor this.	N

Safety signal (no. of times presented to board)	Outcome	Most recent time considered	Explanation	Regulator action
Guillain-Barré Syndrome (GBS) (2)	Possible association. Continue to monitor.	26/01/22	The Board agreed that current evidence does not suggest a side effect of 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
Thrombosis (blood clots) (3)	Unlikely association. Continue to monitor.	02/03/22	The Board agreed that current evidence does not suggest a side effect of thrombosis, and that Medsafe should continue monitoring through routine pharmacovigilance activities.	Y
People with persisting disability (1)	Possible association. Continue to monitor.	09/03/22	The Board noted that symptoms do not necessarily mean persisting disability and were broadly reassured by the data.	N
Pregnancy-related outcomes (2)	Unlikely association. Continue to monitor. See the Monitoring communication.	30/03/22	The Board noted that there was international consensus that there are no pregnancy safety concerns with the Pfizer/BioNTech vaccine. Published studies have not found an increased risk of a range of maternal or neonatal adverse pregnancy outcomes or adverse effects on fertility. The Board was reassured by the information and recommended that Medsafe continue to monitor through routine pharmacovigilance.	Y
Myocarditis/pericarditis (10)	Associated with the vaccine. Information has been added to Comirnaty data sheet. See also the Alert communication.	30/03/22	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 continue to monitor this issue closely.	Y
Thyroid disorders (1)	Unlikely association. Continue to monitor.	30/03/22	The Board commented that the data presented was reassuring. It was noted that the thyroid conditions discussed are readily managed. The Board recommended that Medsafe continue monitoring through routine pharmacovigilance activities.	N

Safety signal (no. of times presented to board)	Outcome	Most recent time considered	Explanation	Regulator action
Tinnitus and hearing loss (2)	Possible association. Continue to monitor.	18/05/22	The Board noted that tinnitus occurs commonly in the general population, with the underlying cause in most cases remaining unknown. The Board agreed there was a hint of a possible association, however the current evidence is not definitive. The Board agreed that Medsafe should continue monitoring through routine pharmacovigilance activities.	N
Vasculitis (1)	Unlikely association. Continue to monitor.	03/08/22	The Board agreed that current evidence does not suggest a side effect of vasculitis, and that Medsafe should continue monitoring through routine pharmacovigilance activities.	N
Acute Kidney Injury (AKI) (1)	Possible association. Continue to monitor.	21/09/22	The Board noted the limitations of the analysis that had identified the increased risk of AKI, specifically around the coded health conditions included. In addition, age, gender, ethnicity, and comorbidities were not adjusted for. The Board noted that a lot of the reported cases had relevant medical history that could increase the risk of developing AKI. The Board agreed with Medsafe's recommendation to continue monitoring through routine pharmacovigilance.	N
Thrombocytopenia (2)	Possible association. Continue to monitor.	21/09/22	The Board noted that thrombocytopenia has not been confirmed as a side effect by any international regulators and there has been no clear association found in real-world studies. Based on the available information, the Board agreed with Medsafe's recommendation to continue monitoring, noting that the current evidence was not strong for a link between the event and the vaccine.	N
Bell's palsy	Associated with the vaccine. Acute peripheral facial paralysis is listed in the data sheet as an adverse reaction.	07/12/22	The Board noted that Bell's palsy is a rare but known adverse reaction of the vaccine. Review of the international literature did not find anything remarkable that impacts the risk/benefit balance and safety profile. The Board agreed that there was no change in the safety of the vaccine in relation to Bell's palsy and Medsafe should continue monitoring through routine pharmacovigilance activities.	N
Herpes zoster (3)	Possible association. Continue to monitor.	07/12/22	The Board agreed that current evidence does not suggest a side effect of herpes zoster, and that Medsafe should continue monitoring through routine pharmacovigilance activities.	N

2.1 Myocarditis and pericarditis

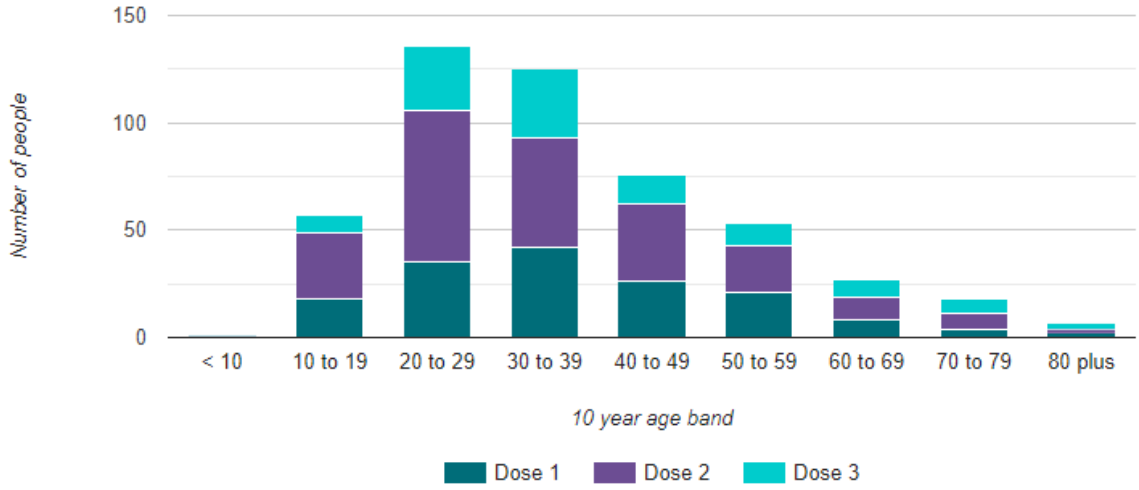
Myocarditis and pericarditis were identified as rare adverse reactions of the Pfizer/BioNTech vaccine in July 2021. This information was first included in the New Zealand data sheet and consumer medicine information for the Pfizer/BioNTech vaccine on 28 July 2021. In 2022, the data sheet was further updated, as shown 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, but not exclusively in younger men. There have been reports in females. Based on accumulating data, the reporting rates of myocarditis and pericarditis after primary series in children ages 5 through < 12 years are lower than in ages 12 through 17 years. Rates of myocarditis and pericarditis in booster doses do not appear to be higher than after the second dose in the primary series. The cases are generally mild and individuals tend to recover within a short time following standard treatment and rest. Cases of myocarditis and pericarditis following vaccination have rarely been associated with severe outcomes including death.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis, including atypical presentations. 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. Non-specific symptoms of myocarditis and pericarditis also include fatigue, nausea and vomiting, abdominal pain, dizziness or syncope, oedema and cough. Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

The Board received 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 31 August 2022, CARM had received 500 reports where there was evidence of a clinical diagnosis of myocarditis or pericarditis and the symptom onset was within 30 days of vaccination. A time period of 30 days was chosen for reporting purposes to reduce the chances of including coincidental cases.

Figure 3: Ages of people with reported myocarditis or pericarditis after the Pfizer/BioNTech vaccine in New Zealand, by dose, up to 31 August 2022



Source: Medsafe. 2021. *Adverse events following immunisation with COVID-19 vaccines: Safety Report #45 – 14 September 2022*. URL: https://www.medsafe.govt.nz/COVID-19/safety-report-45.asp (accessed 05 Jan 2023).

Of the 500 reports, 62% were for males. More reports were received after dose 2, with 31% associated with dose 1, 46% of reports associated with dose 2 and 22% reporting that the myocarditis or pericarditis occurred after dose 3 of the Pfizer/BioNTech vaccine.

There have been 4 reports of likely vaccine-mediated myocarditis with a fatal outcome. The coroner is investigating these reports. See section 6 and section 7 of this report for more information.

2.2 Guillain-Barré Syndrome (GBS)

Guillain-Barré Syndrome (GBS) is an acute monophasic illness causing a rapidly progressing nerve damage in both sides of the body with weakness or paralysis which can last up to 4 weeks before reaching a plateau. The classical presentation of GBS is symmetrical weakness and decreased tendon reflexes in both sides of the body, with or without accompanying sensory symptoms such as numbness or tingling.

An overview of the available information for GBS and the Pfizer/BioNTech COVID-19 vaccine was presented to the Board in August 2021. At this time, post-marketing monitoring had shown increased reporting of GBS with the adenovirus COVID-19 vaccines (AstraZeneca and Janssen). However no biological mechanism was established, and the cases presented for these vaccines did not suggest a causal association.

In contrast, post-marketing monitoring for the Pfizer/BioNTech COVID-19 vaccine locally and internationally has not shown an increase in reporting of GBS. The Board agreed that the current evidence for the Pfizer/BioNTech COVID-19 vaccine does not suggest a side effect of GBS. The

Board recommended that Medsafe continue to closely monitor reports of GBS through routine pharmacovigilance activities.

An update on GBS was provided to the Board in January 2022. At this time, CARM had received 20 case reports of suspected GBS in individuals who had received the Pfizer/BioNTech COVID-19 vaccine. The observed number of cases in New Zealand and internationally for GBS after the Pfizer/BioNTech COVID-19 vaccine was observed to be within the expected background rate. A review of the available literature did not suggest an increased risk of GBS with the Pfizer/BioNTech COVID-19 vaccine. The Board supported Medsafe's recommendation to continue monitoring.

2.3 Bleeding and clotting conditions

In April 2021, the Board considered thrombosis with thrombocytopenia syndrome (TTS) at an extraordinary meeting and concluded that there was no risk of this condition with the Pfizer/BioNTech COVID-19 vaccine. Following a recommendation from the Board, Medsafe issued a Monitoring communication to provide information on the association between TTS and the Janssen and AstraZeneca COVID-19 vaccines.

The Board have considered both thrombosis and thrombocytopenia separately (twice) as potential safety signals for the Pfizer/BioNTech COVID-19 vaccine. Thrombosis is the formation of a thrombus (blood clot) in a blood vessel that can obstruct blood flow through the circulatory system (eg, heart and blood vessels) resulting in several thromboembolic conditions (ie, deep vein thrombosis and pulmonary embolism).

A review of the available information on thrombosis and thromboembolic conditions after Pfizer/BioNTech COVID-19 vaccination in New Zealand and internationally was first presented to the Board on 21 July 2021. At this time, there were 16 reports of clotting type events for the Pfizer/BioNTech COVID-19 vaccine in New Zealand. It was noted that there was no evidence from any international regulators that the Pfizer/BioNTech COVID-19 vaccine was linked to thrombosis. The Board was reassured by this data and agreed with Medsafe's recommendation to continue monitoring through routine pharmacovigilance.

The Board recommended the creation of information for both consumers and healthcare professionals regarding the difference between thrombosis versus thrombosis with thrombocytopenia (TTS). Medsafe published a Consumer Information Leaflet, 'What is Thrombosis with Thrombocytopenia Syndrome (TTS)' and a Dear Healthcare Professional Letter 'AstraZeneca and Janssen COVID-19 vaccines' in November 2021.

Following an increase in the number of reported clotting type events as the vaccine was rolled out more widely in the New Zealand population, an updated review of thrombosis and thromboembolic conditions was presented to the Board on 6 October 2021. At this time, there was no additional international evidence from what the Board had previously considered, and other international regulators (MHRA, EMA, FDA and TGA) had not found thrombosis or

thromboembolic events to be a safety signal for the Pfizer/BioNTech COVID-19 vaccine. The Board agreed that the available information did not suggest a link between the vaccine and thrombotic events and that Medsafe should continue to monitor through routine pharmacovigilance activities.

Due to concerns around the risk of thrombosis after Pfizer/BioNTech COVID-19 vaccination, in addition to Medsafe's monitoring, the Programme commenced a study to evaluate the risk of thrombotic events after Pfizer/BioNTech vaccination in New Zealand. This was conducted as a self-controlled case series (where individuals act as their own control), using national hospitalisation and immunisation records.

An update on this work was presented and discussed with the Board in March 2022, following the identification of a potential signal for lower limb thrombosis. Analysis had shown a statistically significant increased risk for lower limb thrombosis with the Pfizer/BioNTech COVID-19 vaccine. However, venous thrombosis showed the opposite, with a statistically significant decrease in risk observed. As lower limb and venous thrombosis have similar codes in hospital records, the Board's haematologist advised that these codes should be combined. Analysis of the combined codes did not identify a signal. The Board agreed with the approach taken and were reassured by the data presented, which aligns with international evidence. This study has subsequently been published in an international peer-reviewed journal 'Thrombotic events following the BNT162b2 mRNA COVID-19 vaccine (Pfizer-BioNTech) in Aotearoa New Zealand: A self-controlled case series study'.

Thrombocytopenia is a condition where an individual's platelet count in their blood is too low. Platelets are small blood cells that help blood to clot and prevent bleeding. Immune or idiopathic thrombocytopenia purpura (ITP) has been reported after several vaccines and linked to the measles, mumps and rubella (MMR) vaccine. The cause of vaccine-related thrombocytopenia is thought to be immune related, with most cases that develop being self-limiting and resolving with standard treatment. In addition, COVID-19 infection has been linked to both thrombocytopenia and ITP, which highlighted the importance of understanding if there is an association between COVID-19 vaccines and thrombocytopenia.

The Board first considered thrombocytopenia as a potential safety signal for the Pfizer/BioNTech COVID-19 vaccine in August 2021. At this time there were a small number of reports (<6) of thrombocytopenia for the Pfizer/BioNTech vaccine in New Zealand. The Board noted that observed-versus-expected (O/E) analyses (where the occurrence of thrombocytopenia from hospitalisation data in the vaccinated population is compared to the background rate of thrombocytopenia) by both Medsafe and the sponsor had not found an increased incidence of this condition after vaccination. The Board agreed that there was no evidence to confirm a side effect and supported Medsafe's recommendation to continue monitoring through routine pharmacovigilance.

Following a small statistically significant increased incidence of thrombocytopenia being observed in a local O/E analysis for the second dose of the Pfizer/BioNTech vaccine, an updated review of the local and international evidence was presented to the Board for consideration in September 2022. The Board noted the O/E analysis had some limitations, such as, events occurring in primary care not being included and the coding for thrombocytopenia including several unrelated issues (eg, infection and chemotherapy-related thrombocytopenia). Thrombocytopenia has not been confirmed as a side effect of the Pfizer/BioNTech COVID-19 vaccine by international regulators and there has been no clear association found in real-world studies. Based on the available information, the Board agreed with Medsafe's recommendation to continue monitoring, noting that the current evidence was not strong for a link between the event and the vaccine.

2.4 Stroke

The Board considered stroke as an AESI following administration of the Pfizer/BioNTech COVID-19 vaccine twice in 2021. There are 2 broad categories of stroke[1]:

- haemorrhagic strokes: due to bleeding in or around the brain
- ischaemic strokes: due to a blockage cutting off the blood supply to the brain

Approximately 80% of strokes are due to ischaemic cerebral infarction, and 20% to brain haemorrhage.

The available information for stroke and the Pfizer/BioNTech COVID-19 vaccine was first presented to the Board in June 2021. At this time, CARM had received 11 reports of AEFIs related to stroke or cerebrovascular accident (CVA). Although the narratives show a temporal association between the vaccine and event, this does not necessarily mean causality. There have also been reports of stroke in other countries, however, a causal link has not been established.

The Board noted that the number of reported cases is reflective of the low number of people vaccinated (June 2021) and that there is not a spike (which would be concerning). The Board supported Medsafe's recommendation to continue monitoring.

An update on stroke and the Pfizer/BioNTech vaccine was presented to the Board in November 2021. The vaccination programme had commenced in February 2021 and from July 2021 had been rolled out to the general population in New Zealand. Up to 20 October 2021 (data cut-off for presentation) there were 79 reports to CARM for stroke/CVA following administration of Pfizer/BioNTech COVID-19 vaccine. Local O/E analyses with New Zealand data to date did not show an increased risk for stroke.

The Board noted that some studies in the literature showed a weak association between the Pfizer/BioNTech COVID-19 vaccine and stroke, while other studies have not shown an

[1] Caplan LR et al. 2022. Clinical diagnosis of stroke subtypes. In: *UpToDate* 28 June 2022. URL: https://www.uptodate.com/contents/clinical-diagnosis-of-stroke-subtypes (accessed 20 March 2023).

association. Due to the small number of cases and rare outcomes, particularly for cerebral venous sinus thrombosis (CVST), further validation is needed. The Board agreed that data from the literature, sponsor's safety database and O/E analyses did not support a side effect. It was recommended that Medsafe continue to monitor this issue through routine pharmacovigilance.

2.5 Use of the Pfizer/BioNTech vaccine in pregnancy

There remains 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. The Board reviewed the available information for the use of the Pfizer/BioNTech COVID-19 vaccine in pregnancy in 2021 and 2022.

Medsafe first presented the available information to the Board on 27 October 2021. At this time, the Board noted that there were no concerns from the reported events to date for the use of the Pfizer/BioNTech COVID-19 vaccine in pregnant people. The Board also noted that pregnant people with symptomatic COVID-19 infection appear to have an increased risk of a more severe outcomes (eg, ICU admission) in comparison with non-pregnant people of reproductive age and may also be at increased risk of preterm birth. On the recommendation of the Board, Medsafe published a Monitoring communication on 17 November 2021, stating that there are no safety concerns for the use of the Pfizer/BioNTech COVID-19 vaccine in pregnancy.

An update of the available information for the use of the Pfizer/BioNTech COVID-19 vaccine in pregnancy was presented to the Board on 30 March 2022. Since October 2021, the scientific literature supporting the safety of COVID-19 vaccination in pregnancy has accumulated. Published studies have not found an increased risk of a range of maternal or neonatal adverse pregnancy outcomes or adverse effects on fertility. The Board noted that there was international consensus that there are no pregnancy safety concerns with the Pfizer/BioNTech COVID-19 vaccine. The Board were reassured by the information and supported Medsafe's recommendation to continue monitoring through routine pharmacovigilance.

2.6 Boosters

The Programme began offering a booster dose of the COVID-19 vaccine(s) to eligible consumers on 22 November 2021. The Pfizer/BioNTech COVID-19 vaccine was approved for use as a booster dose a minimum of 6 months after completion of a primary series. In January 2022, the recommended interval between the primary series and booster dose was reduced to 4 months by the Immunisation Programme to accelerate the rollout of booster doses and protect against COVID-19 variants. On 4 February 2022, the booster interval was further reduced from 4 to 3 months by the Immunisation Programme.

The Board first considered the available information for boosters in February 2022. At this time, 2 vaccine boosters were available in New Zealand, the Pfizer/BioNTech COVID-19 vaccine and the AstraZeneca COVID-19 vaccine. The AstraZeneca COVID-19 vaccine booster was available

for people 18 years and older (unapproved use), who could not receive the Pfizer/BioNTech COVID-19 vaccine due to medical reasons or for those wanting an alternative vaccine option.

Up to 26 January 2022 (data cut-off for presentation to Board), 1,162,048 booster doses had been administered in New Zealand (1,161,418 doses were for the Pfizer/BioNTech COVID-19 vaccine). At the time of data presentation to the Board, there were 3,646 AEFI reports to CARM after a COVID-19 vaccine booster. The majority of these reports were following the Pfizer/BioNTech COVID-19 booster, given the low uptake of the AstraZeneca COVID-19 vaccine.

Reported adverse events after a booster dose of the Pfizer/BioNTech COVID-19 vaccine followed a similar pattern to those experienced after the 2-dose primary series. Generally, the reporting rates for the most frequently reported adverse events were lower after a booster dose than after doses 1 and 2. The exceptions were both swelling and lymphadenopathy (enlarged lymph nodes), which were reported more frequently after the booster dose (ie, dose 3) than after doses 1 or 2 (Table 2).

Table 2: Most frequently reported adverse events for the Pfizer/BioNTech COVID-19 vaccine – reporting rate per 1,000 vaccines administered, by dose number, up to 23 January 2022

Adverse event	Reporting rate per 1,000 vaccines administered		
	Dose 1	Dose 2	Dose 3 (booster)
Headache	1.59	1.96	1.38
Injection site pain	1.26	1.51	1.35
Lethargy	1.31	1.68	1.33
Lymphadenopathy	0.30	0.69	1.23
Pyrexia	0.49	1.04	0.88
Influenza-like illness	0.53	0.99	0.82
Nausea	1.26	1.20	0.80
Dizziness	2.16	1.44	0.74
Chest discomfort	1.21	1.06	0.57
Swelling	0.28	0.35	0.40

Source: Ministry of Health. Qlik App. *COVID-19 Adverse Events Following Immunisation (AEFI)* (accessed 28 January 2022).

Similar trends have been observed by overseas regulators, and the sponsor has confirmed there is an increased rate of lymphadenopathy following the Pfizer/BioNTech COVID-19 vaccine booster dose. All AESI, including myocarditis and pericarditis, continue to be monitored closely both locally and overseas. A small number of cases of myocarditis and pericarditis had been reported at data-cut off.

An update on boosters was provided to the Board in May 2022. At this time, 3 vaccines were available for use in New Zealand as a booster, with the Novavax COVID-19 vaccine (unapproved use) also being offered. Up to 6 April 2022 (data cut-off), 2,578,275 booster doses had been administered in New Zealand (2,556,544 doses were for the Pfizer/BioNTech COVID-19 vaccine).

There had been 10,704 AEFIs reported to CARM following a COVID-19 booster/third dose. Most of these AEFIs were for expected reactogenicity events (ie, headache, injection site pain, lethargy).

No new safety concerns have been identified with booster doses and the types of AEFIs reported are the same as previously reported with the primary series of the Pfizer/BioNTech COVID-19 vaccine. The Board agreed with Medsafe's recommendation to continue monitoring COVID-19 vaccine boosters through routine pharmacovigilance.

2.7 Tinnitus

Tinnitus is characterised by a ringing or buzzing noise in one or both ears that may be constant or intermittent and is often associated with hearing loss. It is a common problem, affecting about 15% to 20% of people, and is especially common in older adults. Tinnitus affects people differently and for some people, quality of life can be significantly affected. Tinnitus can be caused by an underlying condition (ie, age-related hearing loss or an ear injury) or by other factors, such as exposure to loud sounds, a cold or an adverse reaction to a medicine.

Tinnitus is identified as a very rare adverse reaction in the Janssen COVID-19 vaccine data sheet. However, tinnitus is not listed as an adverse reaction in the Pfizer/BioNTech COVID-19 vaccine data sheet. As there have been reports of tinnitus both locally and internationally with the Pfizer/BioNTech COVID-19 vaccine, an overview of the available data was presented to the Board for consideration in August 2021.

The Board noted that reports were being received after dose 1 and 2 of the vaccine, with varying times to the onset of symptoms (hours to days). There has been no causal link found between the Pfizer/BioNTech COVID-19 vaccine and tinnitus, and the available literature was limited. The Board agreed that the current evidence did not confirm a signal and agreed with Medsafe's recommendation to continue monitoring through routine pharmacovigilance. In the CARM reports, some individuals reported that tinnitus was still present many weeks after vaccination. Therefore, Medsafe requested that the sponsor review tinnitus, with a focus on cases that were persisting (ie, lasting for more than one week).

In May 2022, an update on tinnitus and review of non-tinnitus hearing loss for the Pfizer/BioNTech, AstraZeneca and Novavax COVID-19 vaccines was presented to the Board. Since the previous update to the Board in August 2021, there was a large increase in the number of cases of tinnitus reported to CARM for the Pfizer/BioNTech COVID-19 vaccine (n=822 as of 2 May 2022). However, this increase in reports needed to be considered in the context of a considerable increase in the number of vaccine doses administered between August 2021 and May 2022. There were only a small number of tinnitus cases reported for both the AstraZeneca (n=11) and Novavax (n<10) COVID-19 vaccines.

The Board noted that information on whether symptoms persisted was still missing, with CARM confirming a study would be needed to obtain further detail. Information from the sponsor for

the Pfizer/BioNTech COVID-19 vaccine did not confirm a causal association for tinnitus and hearing loss. From both the local and international data available, Medsafe concluded there was insufficient information to confirm a link between any of the COVID-19 vaccines used in New Zealand and tinnitus. The Board agreed that the evidence was not definitive to confirm an association and supported Medsafe's recommendation to continue monitoring.

2.8 Acute kidney injury (AKI)

Acute kidney injury (AKI) refers to an abrupt decrease in kidney function and can range from minor loss of kidney function to complete kidney failure. AKI is a recognised complication of SARS-CoV-2 and is often present in people with COVID-19 infection who require hospital admission.

An overview of the local and international data for glomerular disease following the Pfizer/BioNTech COVID-19 vaccine was presented to the Board in August 2021. Glomerular disease is a change in the kidney's ability to filter waste and remove extra fluids from the blood. As the available evidence was limited, the Board supported Medsafe's recommendation to continue to monitor glomerular disease through routine pharmacovigilance.

From a preliminary O/E analysis for AKI conducted during the monitoring period 19 February 2021 to 10 February 2022, the number of observed events was greater than the expected for people aged 20 years and older following dose 1, and for all ages following dose 2. Up to 28 August 2022 (data cut-off for presentation), CARM had received 30 reported cases of AKI after the Pfizer/BioNTech COVID-19 vaccine.

The sponsor hasn't investigated AKI as an AESI. AKI has been considered in the context of vaccine-associated enhanced disease (VAED) and vaccine-associated enhanced respiratory disease (VAERD), where only a small number of cases reported AKI. Development of AKI following COVID-19 infection is well documented, however the literature around AKI following vaccination is limited.

The Board noted the limitations of the O/E conducted, specifically around the coded health conditions included. The condition 'unspecified kidney failure' contributed to the results seen, and without a clinical record assessment it's unclear whether this code captures AKI. In addition, age, gender, ethnicity, and comorbidities were not adjusted for in the O/E. However, of the local and international cases reported, many had a relevant medical history that could increase the risk of developing AKI. The Board accepted Medsafe's recommendation to continue monitoring AKI through routine pharmacovigilance.

2.9 Herpes zoster

Herpes zoster (shingles) as a safety signal following vaccination with the Pfizer/BioNTech COVID-19 vaccine was presented and discussed with the Board on 3 occasions throughout 2021 and 2022:

- 10 June 2021 meeting (data cut-off 7 May 2021)
- 15 December 2021 meeting (data cut-off 17 November 2021)
- 7 December 2022 meeting (data cut-off 28 September 2022).

When herpes zoster was first considered by the Board in June 2021, only a small number of cases had been reported to CARM. The Board's review of these locally reported cases as well as the international data did not identify an increased risk of herpes zoster after vaccination. The Board accepted Medsafe's recommendation to monitor herpes zoster through routine pharmacovigilance. Following an update on the available literature and locally reported cases in December 2021, the Board supported Medsafe's recommendation to continue monitoring through routine pharmacovigilance.

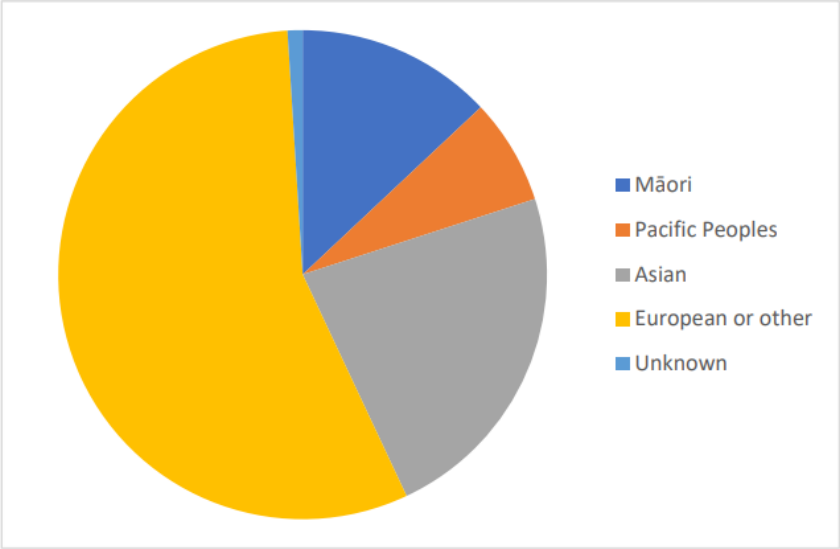
Up to 28 September 2022 (data cut-off for presentation), CARM had received 409 reports of herpes zoster following the Pfizer/BioNTech COVID-19 vaccine. Cases of herpes zoster have also been reported internationally. However, herpes zoster has not been identified as a side effect by other regulators, with no causal link identified. O/E analyses conducted locally and by the sponsor did not find any signs of an association between the vaccine and herpes zoster. The Board were reassured by the data presented and agreed with Medsafe that no regulatory action was needed.

3 Paediatric Pfizer/BioNTech COVID-19

Medsafe provisionally approved the paediatric formulation of the Pfizer/BioNTech COVID-19 vaccine on 16 December 2021. The paediatric formulation is approved for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in children aged 5 to 11 years. The national roll out commenced on 17 January 2022, with the primacy course consisting of 2 doses of the vaccine given at least 21 days apart. The Ministry of Health recommended a minimum 8-week dose interval in this population.

The Board first reviewed the safety data for the use of the paediatric Pfizer/BioNTech COVID-19 vaccine in early February 2022. Between 17 and 30 January 2022 (data cut-off for presentation to the Board), 163,093 doses of the vaccine were administered to children aged 5–11 years. Of the total vaccines administered in this age group, more than 50% were administered to a child of NZ European/Other ethnicity. Combined, Māori (18%) and Pacific (7%) children had received less than 25% of the doses administered. Up to 30 January 2022, the rate ratios of first doses received for Māori and Pacific children compared to other ethnicities were 0.4 and 0.6, respectively. A rate ratio of <1 indicates that Māori and Pacific children are being vaccinated at a lower rate than children of other ethnicities.

Figure 4: Proportion of children aged 5–11 years who have received at least one vaccine dose, by ethnicity, 17–30 January 2022



Up to 30 January 2022, there were 352 AEFI case reports for children aged 5–11 years who had received the paediatric Pfizer/BioNTech COVID-19 vaccine. Of these reports, 96.7% were coded as non-serious. The most frequently reported adverse events were dizziness, nausea, vomiting, pallor, syncope and presyncope. This is a similar pattern to the AEFIs reported by individuals aged 12 years and older for the Pfizer/BioNTech COVID-19 vaccine.

The Board were reassured with the data presented and agreed with Medsafe's recommendation to continue to monitor the safety of the paediatric Pfizer/BioNTech COVID-19 vaccine closely through routine pharmacovigilance, with updates provided to the Board as necessary. The Board did highlight 2 significant concerns that were flagged in a memo to the Programme Steering Group:

- the inequitable roll out to date and the safety implications that this would have in vulnerable populations
- the focus on COVID-19 vaccines has seen other childhood immunisation rates fall substantially, particularly for Māori and Pacific children; this has serious equity implications, along with increasing the risk for an epidemic.

In May 2022, an update on the available information for the paediatric Pfizer/BioNTech COVID-19 vaccine was presented to the Board. Up to 11 April 2022 (data cut-off), 356,699 doses of the vaccine were administered to children aged 5–11 years. Of the total vaccines administered, the proportion of children having received a vaccine and rate ratio by ethnicity remained consistent with the data presented in February 2022.

Up to 11 April 2022, CARM had received 743 AEFI reports for children aged 5–11 years (610 reports for dose 1 and 133 for dose 2). The reporting rate was noted to be lower after dose 2 than dose 1. The overall reporting rate for AEFI was lower for 5–11-year-olds than for those aged 12 years and older. Similar trends have been observed in other countries (eg, Australia). However, this does not mean children are less likely than adults to experience an AEFI, as reporting rates are influenced by different variables (ie, information provided at the time of vaccination or media coverage of a particular event).

At this time, no new safety concerns had been identified with the use of the paediatric Pfizer/BioNTech COVID-19 vaccine in New Zealand or internationally. The AEFIs reported to CARM in this age group are reactions typically associated with vaccination (dizziness, nausea, headache, vomiting) and are similar for dose 1 and 2. The Board supported Medsafe's recommendation to continue monitoring through routine pharmacovigilance.

4 AstraZeneca COVID-19 vaccine

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 to receive a further dose of this vaccine
- preferred a different type of vaccine.

The vaccine became available for use in New Zealand on 26 November 2021. An overview on the use of the AstraZeneca vaccine in New Zealand and adverse events reported locally and internationally was presented to the Board on 26 January 2022. Between 26 November 2021 and 11 January 2022 (data cut-off for presentation), a total of 4,883 AstraZeneca COVID-19 vaccine doses were administered in New Zealand.

At this time, 170 AEFI were reported to CARM with <10 of these reports classified as serious. The most common reported adverse events were headache, lethargy, dizziness, flu-like illness, fever, injection site pain and nausea. Most of the cases classified as serious were associated with anaphylaxis-type reactions[2] with the majority of these people having also had similar reactions to the Pfizer/BioNTech COVID-19 vaccine.

During post-marketing monitoring of the AstraZeneca COVID-19 vaccine internationally there were extremely rare reports of TTS. The AstraZeneca COVID-19 vaccine data sheet now lists TTS as a known adverse reaction. There have been no reports of TTS in New Zealand. However, healthcare professionals and consumers should be aware of the possible symptoms of TTS (refer to section 2.3 of this report). The Board noted that the use of the AstraZeneca COVID-19 vaccine in New Zealand was likely to be different than in other countries and therefore the profile of adverse events reported could be different. The Board was reassured with the data presented and agreed with Medsafe that Medsafe should continue monitoring the safety of the AstraZeneca COVID-19 vaccine through routine pharmacovigilance.

The use of the AstraZeneca COVID-19 vaccine was discontinued in New Zealand on 4 September 2022. There had been no reports of concern or potential safety signals for the vaccine in New Zealand during its use, and hence there were no further dedicated updates on the vaccine's safety to the Board.

[2] Anaphylaxis is a known adverse reaction of the AstraZeneca COVID-19 vaccine.

5 Novavax COVID-19 vaccine

The Novavax COVID-19 vaccine was the third COVID-19 vaccine to be funded in New Zealand and received provisional approval on 4 February 2022. The Novavax vaccine is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals aged 18 years and older. The indication has subsequently been extended to individuals 12 years of age and older (primary series) and as a booster in individuals 18 years and older, at least 6 months after completion of a primary series.

The vaccine became available for use on 13 March 2022. A summary of the local and international safety data for the Novavax COVID-19 vaccine was presented to the Board in May 2022. Between 13 March 2022 and 3 May 2022 (data cut-off for presentation), a total of 3,299 doses of the Novavax COVID-19 vaccine were administered in New Zealand. As of 4 May 2022, there were 42 AEFI reports to CARM for the Novavax COVID-19 vaccine. The most frequently reported adverse events align with the adverse reactions listed in the data sheet and included headache, injection site pain, and muscle aches and pains.

The Board noted that there was limited use of the vaccine both locally and internationally, with most of the post-market safety data being generated from Australia. The sponsor indicated that observed-versus-expected reports for myocarditis and pericarditis (pooled) were shown to be statistically significant following a sensitivity analysis. Although not considered to be a validated signal, the sponsor requested complete case details from the Therapeutic Goods Administration (TGA) in Australia. The TGA were closely monitoring reports of myocarditis and pericarditis with the Novavax COVID-19 vaccine.

The Board supported Medsafe's recommendation to continue closely monitoring the use of the Novavax COVID-19 vaccine through routine pharmacovigilance. They also agreed with the recommendation to take further action as appropriate once the sponsor and TGA concluded their signal investigation for myocarditis and pericarditis.

On 8 September 2022, Medsafe issued an Alert communication stating that a small number of myocarditis and pericarditis cases had been reported internationally with the Novavax COVID-19 vaccine. The sponsor considered that myocarditis and pericarditis may be rare adverse reactions of the vaccine and updated the Novavax vaccine data sheet to include the following text:

Myocarditis and pericarditis have been reported in male and female adults within 14 days of administering NUVAXOVID (see section 4.8 Undesirable Effects).

Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.

Available data cannot determine a causal association with NUVAXOVID.

Vaccinated individuals, parents and caregivers 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.

The risk of myocarditis and pericarditis after a third dose of NUVAXOVID has not yet been characterized.

The Board was updated on myocarditis and pericarditis and the Novavax COVID-19 vaccine at their meeting on 21 September 2022. The Board supported the actions taken by Medsafe.

6 Fatal reports

CARM and Medsafe investigate reports of significant events, including those with a fatal outcome. This process involves:

- verification of the report, to check that there is an identifiable individual who has had a COVID-19 vaccination and the reporter is able to be contacted
- follow up with the reporter for further information – if insufficient information is available for assessment
- follow up with relevant healthcare professional and/or pathologist (if case is with the coroner)
- determination of the likelihood that the vaccine caused the reported events.

All fatal reports received for the COVID-19 vaccines were provided to the Board for review and comment. The investigation process can take some time and is not always successful (eg, if there is no further information about the event(s) known).

Medsafe provided a summary of the reported fatal cases in the COVID-19 vaccine safety reports. Up to and including 30 November 2022, there were 184 deaths reported to CARM after administration of the Pfizer/BioNTech vaccine. Following assessment, it has been determined:

- 163 of these deaths were unlikely related to the vaccine
- 15 deaths could not be assessed due to insufficient information
- 2 cases were under investigation
- 2 deaths were determined by the coroner to be due to myocarditis following the first dose of the vaccine
- 1 death was likely due to vaccine induced myocarditis (awaiting coroner's determination)
- 1 death a link to the vaccine could not be excluded, myocarditis was found at the time of death (awaiting coroner's determination).

By chance and separate to a prior COVID-19 vaccination event, some people will experience new illnesses or die from a pre-existing condition shortly after vaccination, especially if they are elderly. Therefore, in addition to considering reports received by CARM, the review process includes comparing natural death rates to observed death rate following vaccination. This comparison is done to check if there are any specific trends or patterns that might indicate a vaccine safety concern.

In the monitoring period for the Pfizer/BioNTech COVID-19 vaccine (19 February 2021 to 30 September 2022), the observed number of deaths was less than the expected number of natural deaths. Further information on the O/E analyses of deaths for the Pfizer/BioNTech COVID-19 vaccine is available in the COVID-19 vaccine safety reports.

7 Ad-hoc meetings

In addition to regular meetings, 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 Programme
- a report of a serious unexpected event where further expert advice is urgently required by CARM, Medsafe or the Programme.

The Board held 2 ad-hoc meetings in 2022.

7.1 March 2022

The Board met on 2 March 2022 to discuss 2 fatal reports in individuals following COVID-19 vaccination that could be potentially due to the vaccine:

- a young person who passed away after their second dose of the Pfizer/BioNTech vaccine
- an elderly person who passed away after a booster dose of the Pfizer/BioNTech vaccine.

Both cases were previously considered by the Board, with further information sought.

The Board first considered the death of the young person in December 2021. However, further tests were pending, and the Board deemed this information necessary before deciding on the role of the vaccine. The person was found to have myocarditis at the time of death, and they had received a vaccine dose in the weeks prior to their death. From the available information, the majority of the Board agreed that the vaccine was a possible cause of the myocarditis in this person.

The Board agreed 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 COVID-19 vaccine continue to greatly outweigh the risk of such rare side effects. The Board noted COVID-19 infection can cause myocarditis, as well as other serious illnesses, and it remains safer to be vaccinated than be infected with the virus.

The death of the elderly person was previously considered by the Board in February 2022. However, a decision on the role of the vaccine was not reached and further information was sought from the reporter and treating healthcare professional. On receipt of additional information, the Board considered the role of the vaccine in the death of this person to be unclassifiable. The Board noted that there were other factors that could have contributed and/or caused the events leading to the death and unfortunately these had not been excluded.

The Board agreed that the circumstances of this case did not change the known safety profile of the Pfizer/BioNTech COVID-19 vaccine. However, they reiterated the importance of considering the benefits of vaccination versus the potential risk of adverse effects in frail elderly on a case-by-case basis. The Board noted that this information is in the data sheet.

At the 2 March 2022 meeting, the Board also considered a study evaluating the effect of the Pfizer/BioNTech COVID-19 vaccine on thrombotic events, following the detection of a potential signal for lower limb thrombosis. See section 2.3 for more information.

7.2 November 2022

The Board met for an ad-hoc meeting on 2 November 2022 to discuss a fatal case where myocarditis was found and documented by the pathologist in the post-mortem report submitted to the investigating coroner. The Board first considered this case in March 2022 and again in April 2022. At the time of these meetings, limited information was available regarding the circumstances surrounding the death, with the full post-mortem findings still pending.

Following receipt of further information, the Board considered the potential causes of the myocarditis in this person, including the vaccine. The Board noted that there were features of myocarditis, possibly related to the vaccine. However, the Board noted that the reported onset of the myocarditis in this case was later than is typically seen with the Pfizer/BioNTech COVID-19 vaccine. The Board agreed that myocarditis was possibly related to the vaccine.

The Board noted that there were other potential contributing factors relating to the person's death. However, the role of these factors in the death is for the coroner to determine. On balance, the Board agreed that myocarditis could not be discounted in the death of this person.

The Board agreed 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 COVID-19 vaccine continue to greatly outweigh the risk of such rare side effects.

8 CV-ISMB support to Pacific countries

8.1 Participating countries

Since May 2021, New Zealand has been supporting the COVID-19 vaccination campaign in 7 Pacific countries: the Cook Islands, Niue, Tokelau, Samoa, Tonga, Tuvalu and Fiji. This support involved donation of Pfizer/BioNTech COVID-19 vaccine doses and the provision of wraparound vaccine rollout support. The New Zealand Ministry of Health, in partnership with Medsafe and Te Whatu Ora, continues to support these countries with meeting the pharmacovigilance requirements for COVID-19 vaccine donations and also providing technical advice on vaccine safety and investigation of serious AEFIs as required.

During the COVID-19 Vaccine and Immunisation Programme, New Zealand health officials worked with their Pacific counterparts to strengthen the pharmacovigilance capability and capacity. The Cook Islands, Niue and Tokelau received end-to-end support for recording, assessing and reporting all AEFIs, as well as international reporting of AEFIs. Samoa, Tonga, Tuvalu and Fiji were supported with reporting AEFIs to the sponsor (Pfizer), and with accessing medical advice for treatment and management of serious AEFIs.

The Polynesian Health Corridors programme is currently working with relevant stakeholders to explore options to strengthen pharmacovigilance for the Cook Islands, Niue, Tokelau, Samoa, Tonga and Tuvalu.

8.2 Role of the CV-ISMB

In addition to providing advice on the safety of COVID-19 vaccines during the rollout across New Zealand, the CV-ISMB provided support to the 7 Pacific countries that were offered access to New Zealand's COVID-19 vaccine portfolio.

If requested by the Health Authorities in the Pacific countries, the Board provided expert advice for interpretation of COVID-19 vaccine safety data and the significance of that information in relation to the benefit-risk profile of COVID-19 vaccines.

There was also a provision for Health Authorities from the Pacific countries to attend meetings and have discussions with the Board if requested. For example, a member of the Niuean Department of Health attended a meeting in 2022 to discuss COVID-19 vaccine safety data with the Board.

9 Conclusion

The COVID-19 Vaccine Independent Safety Monitoring Board was established early in 2021 to support the safety monitoring processes for the COVID-19 vaccines, primarily through the provision of advice to CARM, Medsafe and the National Immunisation Programme. The data cut-off for this report is 28 November 2022, at which point the Pfizer/BioNTech, AstraZeneca and Novavax COVID-19 vaccines had been available for use in people aged 12 years and older. The paediatric formulation of the Pfizer/BioNTech COVID-19 vaccine, for children aged 5–11 years, was rolled out in January 2022.

Throughout 2021 and 2022, more than 12 million doses of COVID-19 vaccines were administered in New Zealand, with the Pfizer/BioNTech COVID-19 vaccine being the primary vaccine (11,977,450 doses). During this time, there was good engagement from both healthcare professionals and members of the public with reporting adverse events following immunisation to CARM. This has helped CARM, Medsafe and the Programme to investigate and evaluate both individual reports of concern and potential safety signals at the population level.

The Board has considered 24 safety signals for the Pfizer/BioNTech COVID-19 vaccine, which led to 40 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 COVID-19 vaccine. In addition, a safety signal for myocarditis and pericarditis was also investigated for the Novavax COVID-19 vaccine and an alert communication was issued after the sponsor indicated that these may be rare adverse reactions to the vaccine.

The expert advice provided by the Board has been invaluable. Medsafe and the Programme have used the Board's advice to support regulatory action and safety communications about COVID-19 vaccines. It was important for the Board to be independent from the Ministry, Te Whatu Ora and other advisory groups (eg, the group who advised on the purchase of vaccines for New Zealand). In consideration of the safety data presented, the Board could recommend a pause or stop to the rollout of the Programme if the risk/benefit of the COVID-19 vaccines changed. Throughout 2021 and 2022 the benefits of vaccination greatly outweighed the risk of both COVID-19 infection and vaccine adverse reactions.

Moving forward there is a need for an expert immunisation advisory group to provide advice and guidance to the Programme for all vaccines in New Zealand. The World Health Organisation Global Vaccine Action Plan recommended all countries have access to a National Immunisation Technical Advisory Group (NITAG). This was one of the recommendations from the recently released report, Initial Priorities for the National Immunisation Programme in Aotearoa produced by the Immunisation Taskforce. The experience and learnings from the Board will feed into the development of this group.