MINISTRY OF HEALTH
MANATŪ HAUORA

Memo

Myocarditis

Date:	22 July 2021
To:	Dr Ian Town, Chair COVID-19 Vaccine Technical Advisory Group
Copy to:	Dr Ashley Bloomfield, Director-General of Health; Jo Gibbs, National Director - COVID-19 Vaccine & Immunisation Programme
From:	Mr John Tait, Chair – COVID-19 Vaccine Independent Safety Monitoring Board
For your:	Action

Purpose of report

1. To request further information from the COVID-19 Vaccine Technical Advisory Group (CV-TAG) regarding their draft recommendations on the use of the Pfizer-BioNTech mRNA COVID-19 vaccine in the context of the risk of myocarditis and/or pericarditis following vaccination.
2. To highlight the need for clarity around the roles and responsibilities of the COVID-19 Vaccine Independent Safety Monitoring Board (CV-ISMB) and CV-TAG in providing advice to the COVID-19 Vaccine and Immunisation Programme (CVIP).

Background and context

3. Myocarditis is an adverse event of special interest for the COVID-19 vaccines and is being closely monitored by the Centre for Adverse Reactions Monitoring (CARM), Medsafe and the CVIP.
4. Medsafe first presented an overview of myocarditis to the CV-ISMB on 27th May, with further updates provided at subsequent meetings (24th June and 21st July). Following advice from the CV-ISMB, an M² monitoring communication was issued by Medsafe on the 9th June (refer Appendix 1).
5. An update on myocarditis/pericarditis reports was presented to the Board at their regular monthly meeting (21st July). Up to the 20th July, CARM have received 9 cases of myocarditis, 7 cases of pericarditis and 5 cases of myopericarditis. Of the 20 cases (10 females, 10 males), the ages ranged from 24-73 years, with 3 cases in consumers 20-29 years (2 females, 1 male). Fifteen of the reports have occurred after the second dose and five reports have been received following the first dose.
6. The Board was updated that Pfizer had updated their Company Core Data Sheet (CCDS) to include myocarditis as a rare adverse event with the Comirnaty vaccine based on international data and this information would be updated in the New Zealand data sheet; with Medsafe to publish an alert

communication to update prescribers and consumers. Medsafe usual process is to update monitoring communications to either state that the signal was dismissed or that it has been incorporated into the product information.

7. New Zealand is currently not seeing the higher than background rates of myocarditis observed overseas in countries such as the United States, however it is noted that this could be due to our current roll out strategy. The Board was reassured by the current data and at the present time myocarditis is not viewed as an issue of concern impacting the balance of benefits and risks of vaccination with Comirnaty in New Zealand.

8. The Board was made aware of the draft myocarditis recommendations being prepared by CV-TAG; however, these haven't been formally shared with the CV-ISMB for consideration or comment. As the following points relate to safety concern(s) and the Board are not aware of the literature that has guided these recommendations, the Board would like to request copies of the relevant data.

    a. People aged 16-29 years receive their second dose of the Pfizer COVID-19 vaccine 8 weeks after the first dose. Emerging data suggests that a longer interval between doses may reduce the severity of some side effects while conferring the maximum protection from COVID-19.

    b. People aged 16-29 years who require regular clinical review by a cardiologist are advised to discuss the risks and benefits of the first and second doses of the COVID-19 vaccine with their healthcare team.

9. The Board expressed concern around ensuring that both the CV-ISMB and the CV-TAG were aligned, especially when information/advice is being provided to the Director-General, Ministers and to inform policy decisions for the CVIP.

Recommendations

10. The CV-ISMB requests the opportunity to review the recommendations proposed by CV-TAG regarding the risk of myocarditis and/or pericarditis following vaccination, with the relevant supporting evidence.

11. A review is conducted to delineate the roles of the CV-TAG and the CV-ISMB in providing advice to inform policy decisions made for the CVIP.

Mr John Tait
Chair of the COVID-19 Vaccine Independent Safety Monitoring Board

MINISTRY OF HEALTH
MANATŪ HAUORA

Myocarditis Monitoring Communication [link]

Safety Information

Published: 9 June 2021

Monitoring

Patients should **NOT** decline vaccination subject to a monitoring communication. If you have any concerns with your vaccination, please contact your healthcare professional. A monitoring communication does not mean that the vaccine, medicine or medical device causes an adverse reaction.

Myocarditis – a potential adverse reaction to Comirnaty (Pfizer COVID-19 vaccine)

Description
Monitoring finishes on 31 December 2021

Medsafe is investigating a potential risk of myocarditis following vaccination with Comirnaty. The aim of this communication is to encourage further reports to obtain more information on this potential safety concern.

Medsafe has received two reports of myocarditis (inflammation of the heart muscle) and two reports of myo pericarditis (inflammation of the bag like membrane around the heart as well as the heart muscle) following vaccination with Comirnaty. A small number of myocarditis cases have also been reported in some other countries, such as Israel and the United States. The myocarditis in these cases has generally been mild and not required treatment. There is currently no suggestion that these cases are due to the vaccine but Medsafe is collaborating with international medicine regulators on this issue.

Products affected
Additional information
Regulator actions
Reporting

Products affected

Product name	Sponsor
Comirnaty	Pfizer BioNTech

Additional information

Comirnaty is an mRNA vaccine given to prevent coronavirus disease 2019 (COVID-19) in adults and adolescents who are 16 years of age and older.

Myocarditis is an inflammation of the heart muscle wall. There are many possible causes of myocarditis, the most common being viral infection. Over 100 people are discharged from hospital with a principle diagnosis of myocarditis in New Zealand every year. Symptoms may be non specific, such as constant tiredness and weakness or cough, or specific to the heart, such as chest pain or palpitations (a sensation of rapid or irregular heartbeat).

Most reported cases of myocarditis after vaccination with Comirnaty appear to be mild and occur within a week after receiving the vaccine, and the person has recovered without treatment. Predominantly adolescents and young adults have been affected and more commonly males. No causal association with the vaccine has been concluded.

The benefits of the Comirnaty vaccine still outweigh the risks.

Information about Comirnaty, including known side effects, can be found in the consumer medicine information (CMI) and data sheet.

Regulator actions

This issue was discussed with Medsafe's Independent Safety Monitoring Board (ISMB) on 27 May. The recommendation from ISMB was to highlight this potential adverse reaction to Comirnaty as a Monitoring Communication.

Reporting

Please report any case of myocarditis in patients who have been vaccinated with Comirnaty. Please include information on:

- the time between vaccination and onset of myocarditis
- if any treatment was required
- if any other medicines are being taken
- any relevant medical history
- if it occurred after the first or second dose of Comirnaty

Consumers and healthcare professionals are encouraged to report suspected adverse reactions to medicines to the Centre for Adverse Reactions Monitoring (CARM).

Memo

Date:	13 August 2021
To:	Susan Kenyon, Manager Clinical Risk Management, Medsafe
From:	Muireann Walton
Subject:	Comirnaty and thrombocytopenia

DESCRIPTION

As of 31st July 2021, there have been 5 reports of thrombocytopenia following Comirnaty administration in New Zealand.

The purpose of this memo is to review available information on thrombocytopenia and Comirnaty and to consider whether any action is required by Medsafe.

NATURE OF THE SAFETY CONCERN

THROMBOCYTOPENIA

Thrombocytopenia is defined by a low platelet count of less than 150 x 10^9/L [1]. Patients with platelet counts greater than 50 x 10^9/L are often asymptomatic, while a platelet count of 10-30 x 10^9/L may lead to mild symptoms and bleeding with minimal trauma. In rare cases, the number of platelets can be so low (<10 x 10^9 per L), that spontaneous and significant bleeding, bruising and purpura can occur [2]. This can be life threatening and is considered a haematological emergency.

Various disorders and diseases are associated with thrombocytopenia and it is often the first sign of underlying conditions such as malignancies, infectious diseases, and autoimmune disorders. It can also be a side effect of several medicines.

Thrombocytopenia can arise from the following:

- decreased platelet production by bone marrow
- increased platelet destruction
- platelet splenic sequestration; **OR**
- Combination of the above factors [2]

A classification of thrombocytopenia by these mechanisms is shown in table 1.

Notably, immune or idiopathic thrombocytopenia purpura (ITP) has been reported after several vaccines and it has been linked to the MMR vaccine, with a risk window of six weeks [3] The aetiology of vaccine-related thrombocytopenia is considered immune related with antibodies detected on platelets in approximately 79% of cases[3]. The risk of vaccine-related thrombocytopenia is extremely low, and most cases are self-limiting and resolve with standard treatment.

Further, COVID-19 infection has been linked to thrombocytopenia and ITP [4]. This highlights the importance of understanding any associated risk of thrombocytopenia and COVID-19 vaccines in the population.

Table 1. Classification of thrombocytopenia by mechanism [1]

Decreased platelet production
Bone marrow suppression e.g. medicines, chemotherapy, irradiation
Chronic alcohol abuse
Infections e.g. cytomegalovirus, Epstein-Barr virus, hepatitis C virus, HIV, parvovirus B19, rickettsia, varicella-zoster, rubella, mumps
Myelodysplastic Syndrome
Nutritional deficiencies e.g. vitamin B12, folate
Inherited thrombocytopenia's e.g. Bernard Soulier syndrome, May-Hegglin disorder
Bone marrow failure e.g. aplastic anaemia, inherited bone marrow failure syndromes
Neoplastic infiltration of the bone marrow
Increased platelet destruction
Drug-induced thrombocytopenia (DITP) e.g. quinine, penicillin, MMR vaccine, anticonvulsants
Idiopathic thrombocytopenia purpura
Autoimmune destruction: e.g. antiphospholipid syndrome, systemic lupus erythematosus, rheumatoid arthritis
Infections e.g. cytomegalovirus, Epstein-Barr virus, hepatitis C virus, HIV, parvovirus B19, rickettsia, varicella-zoster, rubella, mumps
Mechanical destruction: e.g. mechanical cardiac valve, cardiac bypass
Preeclampsia/HELLP syndrome
Heparin induced thrombocytopenia
Thrombotic thrombocytopenic purpura/ haemolytic uremic syndrome
Alloimmune destruction (post-transfusion, neonatal, post-transplantation)
Disseminated intravascular coagulation/severe sepsis
Sequestration/other
Chronic alcohol abuse
Gestational thrombocytopenia
Hypersplenism
Chronic liver disease e.g. cirrhosis, fibrosis, portal hypertension
Pseudo thrombocytopenia e.g. platelet clumping due to EDTA artefact or fibrin stranding
Dilutional thrombocytopenia e.g. haemorrhage, excess crystalloid replacement

BACKGROUND RATES/EPIDEMIOLOGY IN NEW ZEALAND

THROMBOCYTOPENIA

To investigate how common thrombocytopenia is in New Zealand, background data was searched using the Qlik COVID-19 vaccination background rate app. This application shows publicly funded hospital discharges reported to the National Minimum Data Set (NMDS) since 1 July 2015 (discharges between 1 July 2015 to 1 Aug 2021).

Thrombocytopenia (clinical codes D696, D696, D693 and D694) was selected as adverse events of special interest (AESI). Note that this data only includes cases of thrombocytopenia that were admitted to hospital and does not include cases that did not require admission. Further, only those ages 12 year and older are currently being vaccinated in New Zealand, so the discharge data shown below excludes younger age groups (0-4 years, 4-9 years and 10-14 years).

Figure 1 below shows the number of people discharged with thrombocytopenia per financial year since 2015/216. Since 1 July 2015, there have been 13,967 people aged 15 years and older discharged with a diagnosis of thrombocytopenia and 22,757 hospitalisations. The number is consistent, with 2,000, -3,000 people discharged from hospital with thrombocytopenia annually.

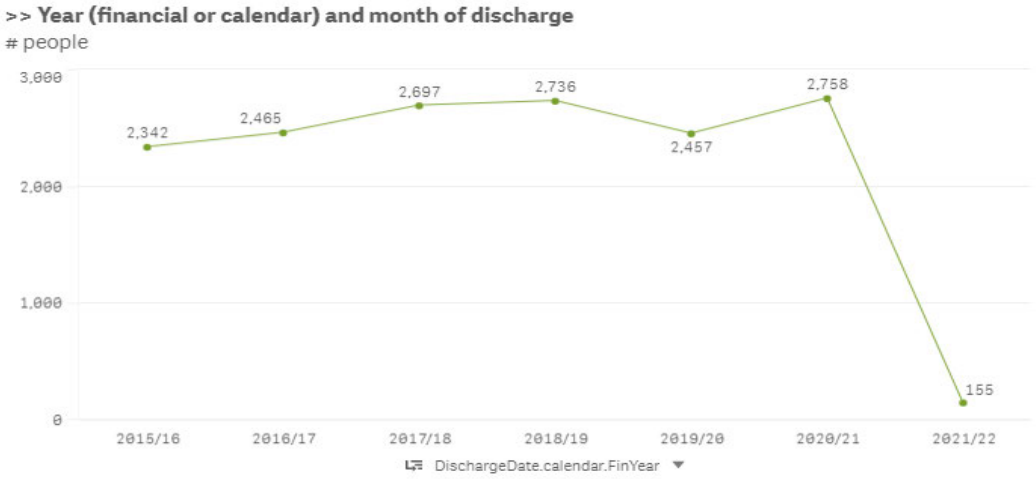

Figure 1: Number of people (≥15 years) discharged with thrombocytopenia, by financial year, 2015/16 to 2021/22. Source: COVID-19 Vaccination Events Qlik app, updated 1 August 2021 (accessed 1 August 2021).

NEW ZEALAND HOSPITALISATION RATES OF THROMBOCYTOPENIA

The incidence rate of thrombocytopenia per 100,000 persons from 2008 to 2019 was calculated to understand the prevalence of the conditions in the New Zealand population by age group. This data was generated by Associate Professor Helen Petousis-Harris and colleagues from the University of Auckland for the SAFE project and is shown below (figures 2-4).

The background rate for the resident New Zealand population was estimated using health, tax, education data tables, from the Integrated Data Infrastructure (IDI) which is carefully managed by Statistics New Zealand (Stats NZ). The counts of thrombocytopenia were selected using the following ICD10 clinical codes: D693, D694, D695, D696, D820, M311.

As per figure 2, there is a clear upward trend of thrombocytopenia with age, with the highest incident rate seen in those aged 80+. Conversely, there is no apparent trend of thrombocytopenia hospitalisation rates by different ethnicities or gender as shown in figures 3 and 4.

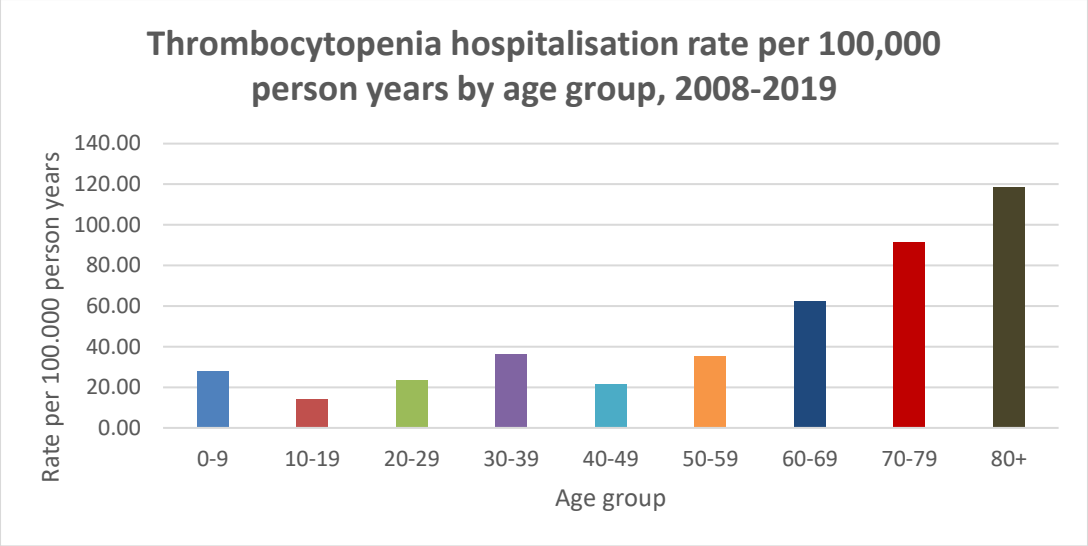

Figure 2. Thrombocytopenia hospitalisation rate per 100,000 persons by age group from 2008-2019.
Source: Preliminary background rates from the UoA SAFE study.

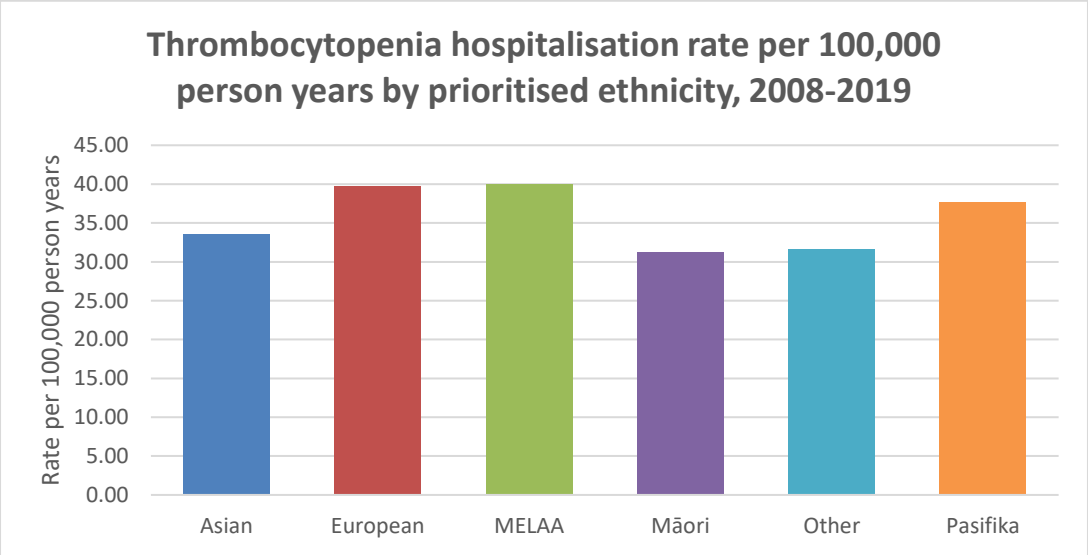

Figure 3. Thrombocytopenia hospitalisation rate per 100,000 persons by ethnicity from 2008-2019.
Source: Preliminary background rates from the UoA SAFE study.

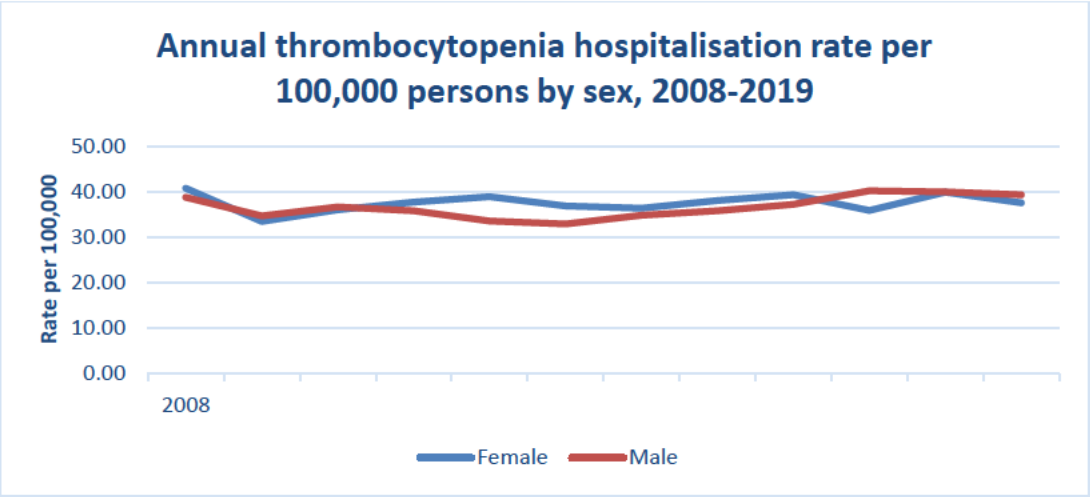

Figure 4. Thrombocytopenia hospitalisation rate per 100,000 persons by sex from 2008-2019.
Source: Preliminary background rates from the UoA SAFE study.

INTERNATIONAL DATA

The Coalition for Epidemic Preparedness Innovations (CEPI) has contracted with the Brighton Collaboration, through the Task Force for Global Health, to harmonize the safety assessment of CEPI-funded vaccines via its Safety Platform for Emergency vACcines (SPEAC) Project. The SPEAC Project has created a list of AESIs relating to vaccines, including thrombocytopenia. This includes summaries of risk factors and background rates for each AESI [5].

The background rates of thrombocytopenia in the United Kingdom and Europe (all countries combined) are shown below. Note that the case definition used for thrombocytopenia to calculate these rates was A: <150,000.

These incidence rates are consistent with the New Zealand background rates above (figure 2), with the highest incidences of thrombocytopenia occurring in the oldest age group.

Table 2. Thrombocytopenia background rates in the UK and Europe [5].

Country [reference]	Study years	Population (age in years)	Incidence rate per 100,000 person years [95% confidence interval] (total cases)		
			All	Males	Females
UK[26] (A)	1990-2005	<18	4.2 [3.7-4.7] (257)	4.7 [3.9-5.5] (148)	3.7 [3.0-4.4] (109)
		18-64	2.9 [2.7-3.2] (534)	2.0 [1.7-2.3] (188)	3.8 [3.4-4.2] (346)
		65-100	7.4 [6.6-8.1] (354)	7.8 [6.6-9.0] (157)	7.1 [6.1-8.0] (197)
European ADVANCE (Accelerated Development of Vaccine benefit-risk Collaboration in Europe) Project[33] (A)					
All country data combined	2003-2014	0-1	20.77 [19.54-22.07]		
		2-4	16.22 [15.30-17.19]		
		5-14	7.15 [6.82-7.49]		
		15-24	9.31 [8.95-9.68]		
		25-44	12.39 [12.11-12.67]		
		45-64	23.76 [23.36-24.17]		
		≥65	53.30 [52.57-54.04]		
		All ages	21.76 [21.57-21.96]		

PRODUCTS

Product name	Sponsor	TT50
BNT162b2 (mRNA) vaccine		
Comirnaty Pfizer-BioNTech	Pfizer New Zealand Limited	TT50-10853

INDICATIONS

In New Zealand, Comirnaty has provisional consent for the following indication:
For the active immunisation to prevent coronavirus disease 2019 caused by SARS-CoV-2, in individuals 12 years of age and over. The use of this vaccine should be in accordance with official recommendations.

USAGE DATA

The New Zealand immunisation programme started on 20 February 2021 with border and MIQ workers and the people they live with. From March, this extended to high-risk frontline workers and people living in high-risk places. Figure 5 below shows the total number of doses administered by 5-year age groups, from 20 February up to and including 5 August 2021. There have been 2,066,369 vaccine doses administered, most of them to individuals aged between 65-69 years.

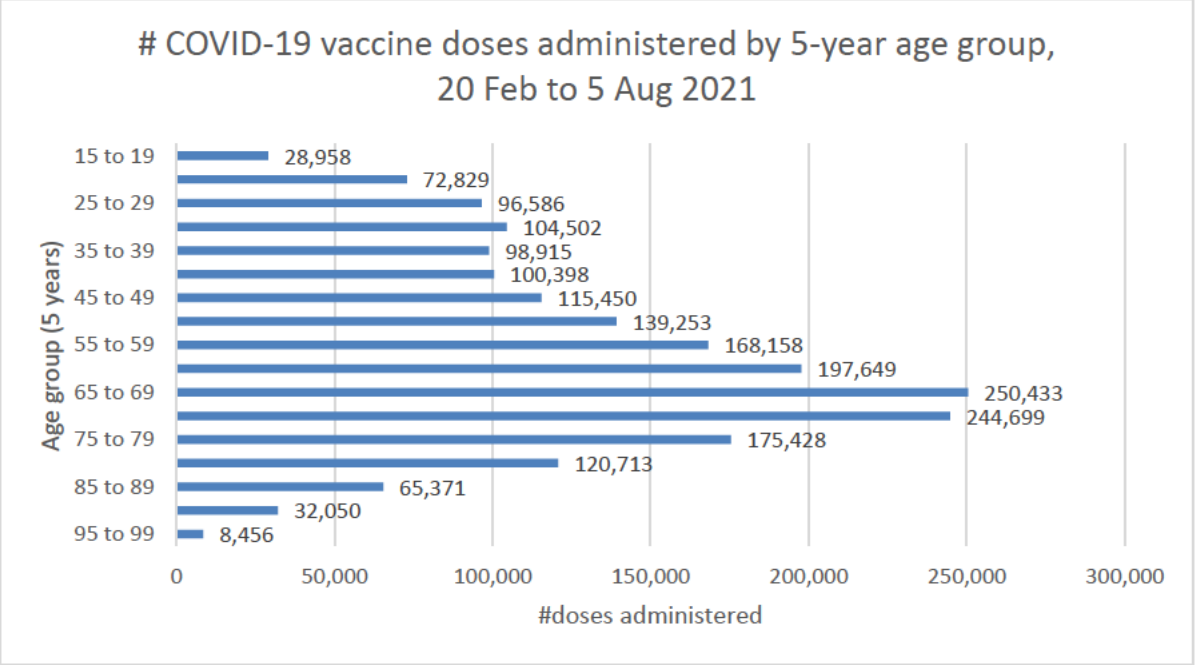

Figure 5: Vaccine doses administered by 5-year age groups, 20 February 2021 to 5 August 2021 (any dose).
Source: COVID-19 Vaccination Events Qlik app, updated 5 August 2021 (accessed 5 August 2021).

HISTORICAL INFORMATION

Thrombocytopenia is not listed in the New Zealand Comirnaty data sheet. This concern has not been previously reviewed.

SOURCE OF SAFETY CONCERN

As at 31 July 2021, there have been 5 reports related to thrombocytopenia. A tabulated summary is provided in Table 3 below. Please refer to Annex 1 – which contains the case narratives.

Table 3. Cases of thrombocytopenia after Comirnaty vaccine reported spontaneously to CARM (up to 31 July 2021).

AEFI-A-	Vaccine date	Date of reaction	TTO (hh:mm)	Gender	Ethnic group	Age	Dose no.	Event	Seriousness	Reported severity	Outcome	Causality assessed ?
AEFI-A-004921	22/03/2021 1:56 pm	7/06/2021 12:50	77 days (2 months, 16 days)	Male	European or other	9(2)(a)	2	Thrombocytopenia purpura (ITP)	Hospitalisation	Severe	Not yet recovered	Unlikely
AEFI-A-005224	2/06/2021	5/06/2021 8:00	3 days	Female	European or other	69	1	Thrombocytopenia	Medically Significant	Moderate	Not yet recovered	Unlikely
AEFI-A-005344	26/05/2021	5/06/2021 17:45	10 days	Male	European or other	9(2)(a)	1	Thrombocytopenia	Emergency Care	Moderate	Recovering	Probable
AEFI-A-007072	6/07/2021	12/07/2021 11:19	6 days	Female	European or other	76	1	Thrombocytopenia	Hospitalisation	Severe	Recovering	Possible
AEFI-A-008370	24/06/2021	21/07/2021 15:49	27 days	Male	European or other	9(2)(a)	2	Thrombocytopenia purpura (ITP)	Hospitalisation	Severe	Recovering	Unclassified-under investigation

REVIEW OF THE AVAILABLE INFORMATION

The above cases (table 3) reported to CARM are presented below by age, gender, ethnicity, and time to occurrence (figure 6). Due to the low number of cases reported, it is difficult to detect any trends, however it appears that thrombocytopenia occurs most commonly after dose 1 than dose 2 and in older age groups.

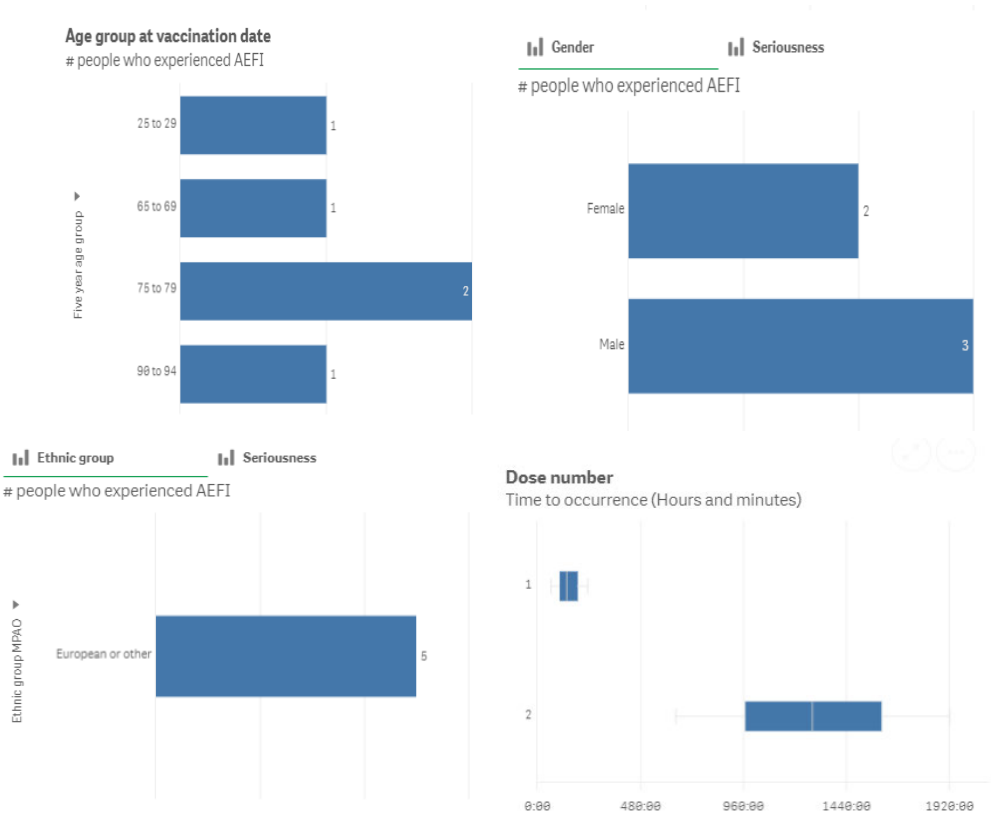

Figure 6. Reports of thrombocytopenia received by CARM presented according to age, gender, ethnicity and time to occurrence.
Source: COVID-19 AEFI Qlik app (accessed 31 July 2021). Terms chosen "thrombocytopenia" or "thrombocytopenia purpura".

OBSERVED VERSUS EXPECTED (O/E) ANALYSES

Observed versus expected analyses was conducted to determine whether the reported counts of spontaneously reported thrombocytopenia following Comirnaty vaccination are higher than expected based on the "natural" background rates of the events in the absence of vaccine exposure in New Zealand.

This analysis is presented in table 4 and shows that the rates of thrombocytopenia following vaccinations did not exceed the number of events we would expect in the background.

There are some limitations to this method and caution is needed when interpreting the O/E rates. The expected rate relies on hospital discharge data from 2008-2019 while the observed counts are likely to be underestimated due to underreporting that occurs with spontaneous surveillance. Incomplete reporting and lags in reporting can further underestimate observe counts.

Table 4. Observed versus expected analyses of spontaneously reported events of thrombocytopenia following Comirnaty in New Zealand

Age	Vaccine doses (1st dose only) administered up to the 31st July 2021	Expected rate per 100,000, Person Years (PY) (2008-2019)	Observed cases	Observed rate per 100,000, Person Years (PY)
10-19	18999	13.96	0	0
20-29	101483	23.42	1	5.45
30-39	124216	36.00	0	0
40-49	137504	21.39	0	0
50-59	193341	35.30	0	0
60-69	284679	62.26	1	3.11
70-79	256243	91.14	2	7.12
80+	134688	118.44	1	6.31
ALL	1,251,153	37.09	5	3.07

REVIEW OF AVAILABLE INFORMATION

CASE REPORTS IN THE LITERATURE

Lee, E. J. et al., (2021). Thrombocytopenia following Pfizer and Moderna SARS-CoV-2 vaccination. [6]

Lee et al., discuss a case series of 20 patients hospitalised due to thrombocytopenia occurring 1–23 days (median 5 days) after vaccination with the Pfizer BioNTech BNT162b2 mRNA Covid-19 vaccine or the Moderna mRNA-1273 SARS-CoV-2 vaccine. Platelet counts at presentation for these cases were generally below 10 × 10^9/L (range 1–36 × 10^9/L; median 2 × 10^9/L). Nine of the patients received the Pfizer vaccine and 11 received the Moderna vaccine. Of these, there were 11 females and 8 males, with ages ranging from 22-73 years old (median 41 years).

The case reports were identified from data available from the Centres for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), agencies of the U.S. Department of Health and Human Services (HHS) Vaccine Adverse Events Reporting System (VAERS), published reports, and via direct communication with patients and treating providers (accessed 29 Jan 2021).

Four of these patients had medical histories of thrombocytopenia, while 3 others had known autoimmune conditions. Of note, a 44-year-old woman was hospitalized for nausea, vomiting and chest pain on the day that she received the Pfizer vaccine. Her laboratory values included a platelet count of 85 × 10^9/L and a peak troponin level of 4 ng/mL (normal < = 0.04 ng/mL). The patient was diagnosed with myocarditis but did not require treatment for thrombocytopenia. Her platelets were 61 × 10^9/L on discharge, but subsequent platelet counts were not reported. Another patient was found to have thrombocytopenia, neutropenia and a pulmonary embolism at an unspecified time following the Pfizer vaccine. This patient was hospitalized and passed away. Unfortunately, no additional details were available.

Overall, the clinical presentations and the favourable response to "ITP-directed" therapies in most of the treated patients, such as corticosteroids and IVIG suggest an antibody-mediated platelet clearance mechanism that is operative in ITP.

Author's conclusions: the authors concluded that an association between ITP and the mRNA COVID-19 vaccines could not be ruled out, especially in those with onset 1-2 weeks after vaccination. One reported case included a patient with a normal platelet count a week prior to vaccination who later developed symptoms 13 days post vaccination which is compatible with vaccine related secondary ITP. Further, all but one case reported occurred after the fist dose of the mRNA vaccines. The authors note that if the vaccine was unrelated to the development of ITP, case occurrences would likely be divided more evenly between the two doses.

However, they noted that approximately 50,000 adults in the US are diagnosed with ITP per year and that the incidence of an immune-mediated thrombocytopenia post vaccination appears either less than or roughly comparable to what would be seen if the cases were coincidental following vaccination. Additional surveillance is therefore needed to determine the true incidence of thrombocytopenia post vaccination.

Welsh, K. L. et al., Thrombocytopenia including immune thrombocytopenia after receipt of mRNA COVID-19 vaccines reported to the Vaccine Adverse Event Reporting System (VAERS) [7]

Welsh et al., describe a case-series study of thrombocytopenia reported to VAERS after vaccination with mRNA COVID-19 vaccines (up to 4 February 2021). Fifteen cases of thrombocytopenia were identified among 18,841,309 doses of Pfizer-BioNTech COVID-19 Vaccine and 13 cases among 16,260,102 doses of Moderna COVID-19 Vaccine. Of these cases, 15 were female, 11 were male and in two the sex was not reported. The median age of cases was 48.5 years and the reported onset time ranged from 1-23 days (median 5.5 days) after vaccination. All but two cases were reported after the first dose of the vaccines. Two patients in this case series died, one of whose death was attributed to intracranial haemorrhage secondary to ITP. The second patient who died reportedly experienced acute myocardial infarction, a pulmonary embolism, and thrombocytopenia although minimal additional case details are available.

The reporting rate of thrombocytopenia was 0.80 per million doses for both vaccines. Based on an annual incidence rate of 3.3 ITP cases per 100,000 adults in the US, the study found that the observed number of thrombocytopenia cases following administration of mRNA COVID-19 vaccines was not greater than the number of ITP cases expected.

Author's conclusions: the author's concluded that the number of reported cases of thrombocytopenia to VAERS does not currently suggest a safety concern attributable to mRNA COVID-19 vaccines.

King, E. R. et al., A Case of Immune Thrombocytopenia After BNT162b2 mRNA COVID-19 Vaccination [8]

King et al., describe a case of a 39-year-old female who developed a petechial rash on her trunk, legs and arms, and fatigue and muscle aches 3 days after receiving her second dose of Comirnaty. She was admitted to hospital and a peripheral smear showed profound thrombocytopenia, with a platelet count of 1000/μL. Several causes of ITP such as viral hepatitis HIV and H. pylori were tested during the patient's hospital stay. All tests returned negative results. Evans syndrome was also ruled out.

The patient was treated with 2 units of platelets, 2 infusions of IV immunoglobulin, and IV methylprednisolone. Her platelet count increased to 92,000/μL on the day of discharge and she was prescribed a tapered dose of oral prednisone. One day later, her rash had resolved, and her platelet count was 243,000/μL. The patient recovered completely with no complications.

The patient's medical history included polycystic ovary syndrome, for which she took norgestimate-ethinyl estradiol. She had no pertinent family or travel history and no history of use of tobacco or alcohol or of substance abuse. The patient had a complete blood count (CBC) and differential 5 months before, which was within normal limits. At that time, she also was tested for COVID-19 antibodies; the results were negative. The patient did not have any illnesses or known COVID-19 exposures before the incident reported here.

Author's conclusions: the author's concluded that due to the lack of medications or conditions that could have caused the condition in the patient, the development of ITP was likely due to the Comirnaty vaccine.

Ganzel, C. and E. Ben-Chetrit (2021) – Immune Thrombocytopenia Following the Pfizer-BioNTech BNT162b2 mRNA COVID-19 Vaccine [9]

Ganzel et al., report a case of a 53-year-old male who was admitted to Shaare Zedek Medical Center in Jerusalem due to epistaxis and low platelet count 2 weeks after receiving the first dose of the Pfizer COVID-19 vaccine.

Medical history included, morbid obesity, diabetes, and hypertension for which he was treated with lercanidipine, losartan, doxazocin, hydrochlorothiazide and aspirin. He took two tablets of levofloxacin for suspected otitis one week prior to admission. He had previously taken levofloxacin on several occasions.

Physical examination revealed wet purpura on his palate and petechial and purpuric rash on the trunk and limbs. His blood count and smear were remarkable for severe thrombocytopenia: 1×10^3 /μL (normal range $150–400\times10^3$ / μL). He was diagnosed with immune thrombocytopenia purpura (ITP). The patient was treated with dexamethasone 20 mg/d and intravenous immunoglobulins, 1 g/kg, with a gradual increase in platelets. Five days later his platelet counts normalised. Due to the severity of the thrombocytopenia, the second dose of the vaccine was not given to the patient.

Author's conclusions: the authors suggest that there may be a temporal relationship between the development of ITP and receipt of the Comirnaty vaccine in this patient. However, they note that levofloxacin has been associated with severe thrombocytopenia. They considered this causality unlikely due to the patient's prior exposure.

Kragholm, K., et al., (2021). Thrombocytopenia after COVID-19 vaccination [10]

This study reviewed cases of thrombocytopenia reported from the North Denmark Region (capture population≈600,000 inhabitants) among healthcare professionals ≤65 years of age following PfizerBioNTech/Moderna (N = 11,689) or the Oxford-AstraZeneca (N = 16,509) COVID-19 vaccinations.

Of 2,130 individuals with post-vaccination platelet measurements available, 50 (40 women and 10 men) had thrombocytopenia (platelet count $<145\times10^9$/L in men and $<165\times10^9$/L in women). Among 1,873 women, 24/813 (3.0 %) vaccinated with the Oxford-AstraZeneca COVID-19 vaccine versus 16/1060 (1.5 %) vaccinated with PfizerBioNTech/Moderna COVID-19 vaccines had thrombocytopenia, odds ratio [95 % confidence interval] for thrombocytopenia of 1.99 [1.05–3.76] for Oxford-AstraZeneca versus PfizerBioNTech/Moderna. Among 257 men, the corresponding odds

ratio [95 % confidence interval] was 0.49 [0.14–1.79]. Severe thrombocytopenia (platelet count <50 × 10^9/L) was seen in three patients vaccinated with Oxford-AstraZeneca (all women between 50 and 60 years of age) versus none among the PfizerBioNTech/Moderna vaccines

Author's conclusions: the author's concluded that thrombocytopenia appears to be significantly more frequent among women vaccinated with Oxford-AstraZeneca COVID-19 when compared to those vaccinated with the PfizerBioNTech/Moderna COVID-19 vaccines. Cases of severe thrombocytopenia were seen only among women vaccinated with the Oxford-AstraZeneca COVID-19 vaccine.

PFIZER/BIONTECH COMIRNATY PSUR MAY 2021

The sponsor is currently submitting a monthly Periodic Safety Update Report (PSUR) for Comirnaty to Medsafe. Their latest reporting interval is 1 June 2021 to 30 June 2021.

Immune Thrombocytopenia (ITP) was previously reviewed by the sponsor in January 2021 and following further reports in the safety database and a request from other regulators (EMA and FDA), it has been re-reviewed in the current PSUR.

Table 5 shows the sponsor's evaluation of new information received related to thrombocytopenia during the reporting interval.

The sponsor has also provided a tabulated summary (during the interval and cumulatively) of serious and non-serious adverse reactions from post-market spontaneous data sources (see Table 6).

Table 5. PSUR June 2021 (1 May 2021 to 31 May 2021): thrombocytopenia events

Haematological AESIs *Search criteria: Leukopenias NEC (HLT) OR Neutropenias (HLT) OR PT Thrombocytopenia OR SMQ Haemorrhage terms (excl laboratory terms)*	• Number of cases: 4319 (5.9% of the total PM dataset, compared to 4.1 % in the previous reporting period), of which 1127 medically confirmed and 3192 non-medically confirmed; • Country of incidence: UK (2774), US (326), Japan (235), France (150), Netherlands (98), Germany (97), Italy (94), Canada and Spain (58 each), Sweden (51), Australia (35), Mexico (33), Finland and Norway (24 each), Czech Republic (23), Belgium (22), Portugal (21), Switzerland (18), Austria and Greece (17 each), Hong Kong and Poland (14 each), Ireland (13), Denmark (12), Hungary and Romania (9 each), Israel (7), Brazil (6), Estonia, Latvia, Lithuania, Luxembourg (5 each), Bulgaria, Iceland, Slovakia, Slovenia and South Africa (4 each); the remaining 20 cases originated from 14 different countries; • Subjects' gender: female (3510), male (669) and unknown (140); • Subjects' age group (n = 3658): Adult (2955), Elderly (671), Adolescent (32); • Number of relevant events: 4922, of which 2002 serious, 2920 non-serious; • Most frequently reported relevant PTs (>10 occurrences) include: Heavy menstrual bleeding (1265), Contusion (550), Epistaxis (410), Vaginal haemorrhage (375), Intermenstrual bleeding (336), Haemorrhage* (199), Thrombocytopenia* (160), Vaccination site bruising (146), Petechiae (109), Purpura (92), Haematoma (85), Postmenopausal haemorrhage (83), Vaccination site haemorrhage (69), Haematochezia (65), Vaccination site haematoma (60), Immune thrombocytopenia* (55), Conjunctival haemorrhage (49), Haemoptysis (47), Eye haemorrhage (41), Haemorrhage subcutaneous (36), Gingival bleeding (34), Blood urine present (30), Haematuria and Rectal haemorrhage (29 each), Internal haemorrhage (28), Haematemesis (26), Genital haemorrhage (21), Injection site bruising (20), Ecchymosis and Increased tendency to bruise (18 each), Gastrointestinal haemorrhage and Skin haemorrhage (17 each), Diarrhoea haemorrhagic (15),

AESIs[32] Category	Post-Marketing[12] Cases Evaluation Total Number of Cases in the Reporting Period (N=73166)
	Melaena and Mouth haemorrhage (13 each), Eye contusion, Lymphopenia, Neutropenia, and Subdural haematoma (12 each); • Relevant event onset latency (n = 3364): Range from <24 hours to 352 days, median = 3 days; • Relevant event outcome[36]: fatal (63), resolved/resolving (1973), resolved with sequelae (46), not resolved (1558) and unknown (1354). * Observed/Expected analysis was performed for Haemorrhage, Immune thrombocytopenia and Thrombocytopenia (see Appendix 5.1). Conclusion: No signals for the hematological AESIs have emerged based on a review of these cases, or of the Observed versus Expected analysis. It should be noted that Menstrual disorders are under review for inclusion in PSUR #1 as requested by EMA.

Table 6. Interval and cumulative count of various MedDRA PT related to thrombosis/thromboembolic events from post-market spontaneous data

MedDRA PT	Serious	
	Interval	Cumulative
Immune thrombocytopenia	55	210
Thrombocytopenia	158	555
Thrombocytopenia purpura	11	21
Thrombotic thrombocytopenia purpura	14	25

Observed versus expected analysis:

The sponsor performed an observed versus expected analysis (O/E) for ITP (see table 7 for preferred terms used). O/E is conducted by the sponsor to determine whether the reported counts of spontaneously reported AESIs are higher than expected based on the background rates of the AESIs in the absence of vaccine exposure.

The analysis below is reported cumulatively for the period since the vaccine was granted provisional approval (9 December 2020 in the US) and for the June reporting interval (1 June 2021 to 30 June 2021). The exposure time was calculated using a 21-day risk window and no risk window for both the reporting interval and the cumulative period. The risk window is defined as the period which one is expected to be at risk of a given event if there is a causal association between the event and the vaccine. The 21-day risk window is an estimate assuming a more acute onset, while the no risk window is a more latent onset.

Note that the limitation to O/E analysis is that the observed counts are likely to be underestimated due to underreporting that occurs with spontaneous surveillance. Incomplete reporting and lags in reporting can further underestimate observe counts.

The background rates used in this analysis are derived from US healthcare databases and regional studies published in the literature. The O/E analysis is presented in tables 8-12.

Table 7. The preferred terms used to identify the spontaneously reported AESI

AESI	PTs
Idiopathic thrombocytopenia purpura, autoimmune thrombocytopenia	Immune thrombocytopenia, thrombocytopenia, thrombotic thrombocytopenia purpura, thrombocytopenia purpura

Table 8. O/E ratios of spontaneously reported events of ITP, autoimmune thrombocytopenia

AESI	21-day risk window (cumulative)		No risk window (cumulative)		21-day risk window (interval)		No risk window (interval)	
	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI
ITP	0.104	0.097, 0.112	0.035	0.033, 0.038	0.143	0.125, 0.163	0.166	0.145, 0.189

Table 9. O/E analyses of spontaneously reported events of ITP, autoimmune thrombocytopenia (cumulative)

AESI	Background rate per 100,000 Person Years (PY)	Obs cases (cumulative)	Exp cases, 21-day risk window (cumulative)	Exp cases, no risk window (cumulative)
ITP	21.46	764	7,334.8	21,785.6

Table 10. O/E analyses of spontaneously reported events of ITP, autoimmune thrombocytopenia (interval)

AESI	Background rate per 100,000 Person Years (PY)	Obs cases (interval)	Exp cases, 21-day risk window (interval)	Exp cases, no risk window (interval)
ITP	21.46	255	1,574.0	1,357.2

Table 11. Age-stratified O/E analyses of spontaneously reported events of ITP, autoimmune thrombocytopenia in European Economic Area Countries and the United States Inputs, 21-Day Risk Window, Interval

AESI	<17 years		18-24 years		25-49 years		50-59 years		60-69 years		70+ years	
	Obs cases	Exp cases	Obs cases	Exp cases	Obs cases	Exp cases	Obs cases	Exp cases	Obs cases	Exp cases	Obs cases	Exp cases
ITP	1	14.4	2	26.4	30	172.8	14	188.4	31	202.2	64	281.7

Table 12. Age-stratified O/E analyses of spontaneously reported events of ITP, autoimmune thrombocytopenia in European Economic Area Countries and the United States Inputs, 21-Day Risk Window, Cumulative

AESI	<17 years		18-24 years		25-49 years		50-59 years		60-69 years		70+ years	
	Obs cases	Exp cases	Obs cases	Exp cases	Obs cases	Exp cases	Obs cases	Exp cases	Obs cases	Exp cases	Obs cases	Exp cases
ITP	7	47.5	10	114.6	89	759.8	54	884.9	71	1,331.2	266	3,537.8

***Sponsor's conclusion*:** the sponsor concluded that no new safety signals have emerged based on this review of the cases, or of the O/E analysis performed. Surveillance will continue.

REGULATORY REVIEW

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY (UK) (MHRAUK)

The MHRA publishes a weekly summary of Yellow Card reporting. The most recent report covers the period 9 December 2020 to 28 July 2021. The report did not note any specific comments or issues related to Comirnaty vaccinations and thrombocytopenia. An extract of their latest Comirnaty 'Vaccine Analysis Print' is shown below in table 12 and represents all UK spontaneous reports relating to thrombocytopenia received between 9 December 2020 and 21 July 2021 for the Comirnaty vaccine.

Table 13. All UK spontaneous reports with various MedDRA PT for thrombocytopenia received between 9/12/20 and 21/07/21 for the Comirnaty vaccine.

Reaction Name	Total	Fatal
Thrombocytopenias		
Immune thrombocytopenia	63	0
Thrombocytopenia	155	1
Thrombocytopenic purpura	4	0
Thrombotic thrombocytopenic purpura	5	0

European Medicines Agency (EMA)

The EMA publishes a monthly COVID-19 vaccine safety update for Comirnaty. In their COVID-19 safety update for Comirnaty dated 29 March 2021, immune thrombocytopenia (ITP) was mentioned.

The EMA stated that "for all COVID-19 vaccines used in the EU, a specific PRAC assessment of immune thrombocytopenia (ITP, low blood platelet levels that can lead to bruising and bleeding) as a suspected side effect is ongoing. The PRAC assessment of the ITP cases reported to EudraVigilance (see section 3) for Comirnaty from vaccination campaigns did not reveal a pattern confirming a causal relationship of ITP with Comirnaty. In some cases, the time-to-onset of symptoms was inconsistent with the possibility of a vaccine-mediated immune reaction".

US Food and Drug Administration (FDA)

Thrombocytopenia is not listed on the 'FDA Comirnaty fact sheet and product labelling '.

The Advisory Committee on Immunisation Practices (ACIP) holds three meetings each year at the Centres for Disease Control and Prevention (CDC). At a meeting on the 23 June 2021, preliminary results from their VSD Rapid Cycle Analysis (RCA) were presented. ITP was chosen as an AESI for this analysis and the results are shown below (see table 13).

Table 14. Outcome events in the 21-day risk interval after either dose of any mRNA vaccine compared with outcome events in vaccinated comparators on the same calendar day (as of 12 July 2021).

Pre-specified outcome event	Events in risk interval	Adj Rate Ratio*	95% CI	Signal
Immune thrombocytopenia	45	1.03	0.59 - 1.85	no

Therapeutic Goods Administration (TGA)(Australia)

Immune thrombocytopenia is continuously monitored as an AESI by the TGA.

The TGA releases weekly COVID-19 vaccine safety report. There is no mention of thrombocytopenia in their weekly report for Comirnaty dated 29 July 2021.

COMMENTS: International regulatory authorities have not recognised thrombosis/thromboembolic conditions as adverse events associated with Comirnaty.

According to publicly available information, various regulatory authorities are continually monitoring for thrombocytopenia as an AESI. To date, they have not seen a higher rate than usual.

PUBLIC INTEREST

There is significant public and media interest in this topic, with accounts of thrombocytopenia following COVID-19 vaccination published on social media platforms.

For example, public alarm was heightened in the US following the death of a 56-year-old male from a haemorrhagic stroke, secondary to ITP who had received the Comirnaty vaccine. This was reported in several US news outlets including the New York Times [11] [12].

EXPERT ADVICE

No expert advice has been sought by external committees or other experts yet.

PROPOSED ACTIONS

Medsafe should continue to monitor for thrombocytopenia through routine pharmacovigilance.

This includes monitoring New Zealand AEFI reports, plus information from the published literature, company reports (e.g., PSURs), and reports and reviews from other regulatory authorities.

CONCLUSIONS

In conclusion, there is currently insufficient information to confirm a possible signal of thrombocytopenia with the use of Comirnaty.

As of 31 July 2021, CARM has received 5 cases of thrombocytopenia following administration of Comirnaty. Two of the cases were reviewed as unlikely related to the vaccine, two were possibly related and one is unclassified, awaiting further investigation. Although a temporal association

between the vaccine and thrombocytopenia was found in some cases, this does not necessarily mean there is causality.

Thrombocytopenia is currently being monitored as an AESI by Medsafe and other global regulators such as the MHRAUK, FDA, EMA and TGA. To date, a causal relationship has not been established between the AESI and Comirnaty by any global regulatory authority.

Further, the observed versus expected analysis performed using New Zealand data, indicates that there has not been an increase in the rate of thrombocytopenia compared to the background rate. This is also supported by the sponsor's O/E analysis and literature based on global data.

It is recommended that Medsafe continue to monitor this issue through routine pharmacovigilance activities. This includes monitoring New Zealand case reports, company safety reports, action from other regulators and information in the literature.

RECOMMENDATIONS

It is recommended that:

1.	This topic is presented to the COVID-19 Vaccine Independent Safety Monitoring Board (ISMB).	Yes
2.	This topic is monitored through routine pharmacovigilance.	Yes

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APPENDIX 1.

COVID-CARM CASE NARRATIVES

AEFI-A-004921: is a report of a 25-year-old male who developed symptoms of idiopathic thrombocytopenia purpurea (ITP) approximately 77 days post 2nd dose of the Comirnaty vaccine (reporter unsure of exact dates). Platelets <10 - Hospital review reports that had viral URTI week prior to onset. The Medical Assessor classified the incidence of ITP as unlikely related to the vaccine.

AEFI-A-005224: is a report of a 69-year-old female who started feeling unwell with nausea, weakness, lethargy and flu-like symptoms 4 days following the first dose of the Comirnaty vaccine. She was seen on 11/06 (Day 10 post vaccination) and identified as having a UTI.
Past medical history; Known myelodysplastic syndrome, on Ruxolitinib 5mg twice daily since October 2020, which has been holding her blood and platelet count at a much better level. On fortnightly bloods, and sudden drop in Hb and platelets in last sample, with also worsening neutropenia.
Treated empirically with nitrofurantoin 50mg qds which she took for 3 days until 14/06. Urine sample sent off on 14/06 - no infective organism. 14/06 had bloods taken : Observation date/time: 14/06/2021 16:15 HAEMOGLOBIN: *** 89 g/l (115 - 155) HCT (first: PCV): *** 0.27 L/L (0.35 - 0.46) MCV: 99 fL (80 - 99) MCH: 33 pg (27 - 33) WBC: *** 1.6 x10E9/L (4.0 - 11.0) DIFFERENTIAL Neut Seg: *** 0.6 x10E9/L (1.9 - 7.5) Lymphocyte: *** 0.8 x10E9/L (1.0 - 4.0) Monocyte: 0.2 x10E9/L (0.2 - 1.0) Eosinophil: < 0.1 x10E9/L. Seriousness details classified as thrombocytopenia and anaemia with neutropenia. The Medical Assessor classified the incidence of thrombocytopenia as unlikely related to the vaccine.

AEFI-A-005344: is a report of a 75-year-old male who had symptoms of abdominal pain/discomfort, nausea and pain in the legs 10 days following the first dose of the Comirnaty vaccine. He also developed neutropenia, lymphopenia, thrombocytopenia and arthralgia.
Past medical history; 2010 rectal ca, high transverse resection Dukes B stable cyst on the pancreas
The case was classified as 'non-serious' and 'moderate severity'.
The Medical Assessor classified the incidence of thrombocytopenia as probably related to the vaccine.

AEFI-A-007072: is a report of a 76-year-old female who developed gastrointestinal bleeding and bruising due to severe thrombocytopenia 6 days following the first dose of the Comirnaty vaccine. Patient required high dose steroids, intravenous immunoglobulin and platelet transfusions. Dry Cough preceding 5/52 (pre-dates Vaccination). Commenced Prednisone 2/7 before onset of blood-stained stools (subsequently found Platelets =16). Noted to have had COVID vaccination 6/7 prior to onset of ITP. Found +ve for RSV as cause of cough. Question mark of whether viral infection as cause of ITP.
The Medical Assessor classified the incidence of thrombocytopenia as probably related to the vaccine.

AEFI-A-008370: is a report of a 92-year-old male who noticed significant bruising with slight knocks. Presented to ED, found to have thrombocytopenia. Thought to be ITP. Has been discharged from hospital - ongoing condition unknown. Case still under review by the Medical Assessor - requested follow up information.
Past medical history; AF Sigmoid polyps Glaucoma BPH Falls

Memo

Date:	15 December 2021
To:	Susan Kenyon, Manager, Clinical Risk Management, Medsafe.
From:	Mariana Traslosheros Reyes, Advisor Pharmacovigilance, Post-Event, COVID-19 Vaccine and Immunisation Programme.
Subject:	ME/CFS following Comirnaty: Review of Available Literature and Adverse Event Reports in New Zealand.
Incident ID:	**Lotus Notes Location:**
For your:	Action: [√] Decision: [√] Information: [√]

Description

There has been interest in the potential for myalgic encephalomyelitis (ME), more commonly known as Chronic Fatigue Syndrome (CFS), or better classified as ME/CFS, as an adverse event following immunisation (AEFI) with the Comirnaty vaccine, both as a new condition and as a relapse or flare up of symptoms in those previously diagnosed with ME/CFS.

This memo provides an update on the information currently available on this issue and considers whether any further action is required.

Nature of the Safety Concern

There is significant public interest in the safety of Comirnaty for those diagnosed with ME/CFS.

Products

Product name	***Sponsor***	***TT50***
BNT162b2 (mRNA)		
Comirnaty	Pfizer New Zealand Limited	TT50-10853

Indications

In New Zealand, Comirnaty has provisional consent for the following indication:

For the active immunisation to prevent coronavirus disease 2019 (covid-19) caused by SARS-CoV-2, in individuals 5 years of age and over.

The use of this vaccine should be in accordance with official recommendations.

USAGE DATA

In New Zealand, Comirnaty is approved for use in individuals aged 12 years and older. Recently the Comirnaty paediatric vaccine has been approved for usage in those aged 5-11 years. The New Zealand immunisation programme started on 20 February 2021 with border and MIQ workers and the people they live with. The programme was expanded in stages to include the general population over aged 12 years and over. In December 2021 the booster roll-out began in people aged 18 years and over. From January 2022, the paediatric vaccine roll-out began in children aged 5-11 years.

As at January 21 2022, 8,892,113 doses of Comirnaty have been delivered in New Zealand to eligible age groups, this includes 51,759 first doses to those aged 5-11 years.

DATA SHEETS

ME/CFS is not mentioned in the Comirnaty data sheet.

This information is consistent with international data sheets.

SOURCE OF SAFETY CONCERN

There has been public interest in the safety of Comirnaty in those with ME/CFS.

REVIEW OF THE AVAILABLE INFORMATION

ME/CFS [1]

ME/CFS is characterised primarily by persistent and debilitating fatigue. ME/CFS can vary in severity from mild to very severe. About one fifth of patients report severe presentations. There is no universally accepted definition for ME/CFS. The usage of the term myalgic encephalomyelitis is questioned as there is limited pathological evidence of brain inflammation in patients with ME/CFS. Similarly, the term Chronic Fatigue Syndrome is contested by those with ME/CFS as it is viewed as too broad. ME/CFS is the most commonly accepted name.

The National Institute for Health and Care Excellence guidelines for physicians suggest that debilitating fatigue that is worsened by any degree of physical, cognitive, or emotional activity, and is not relieved by rest; post-exertional malaise, unrefreshing sleep and/or disturbed sleep; and cognitive difficulties must all be present for patients to be diagnosed with the disorder. Diagnosis must also include the exclusion of an alternative diagnosis and the persistence of symptoms for 3 months.

Research into the aetiology of ME/CFS remains inconclusive. Viral infection has been identified as a cause in some cases, but ME/CFS is distinct from post-illness fatigue and there is limited understanding of how infection results in the chronic nature of ME/CFS.

Importantly ME/CFS has a significant impact on the quality of life of an individual suffering from it. ME/CFS patients report delayed diagnosis and a lack of support from healthcare professionals. Previous misclassifications of ME/CFS have exacerbated prejudices against those with ME/CFS leading to inadequate healthcare. The Associated New Zealand ME Society (ANZMES) reports that the prevalence of ME/CFS in New Zealand is 1 in 250 adults and 1 in 134 children or adolescents. This totals to 25,000 individuals with ME/CFS in New Zealand.

Reports of ME/CFS in New Zealand following Comirnaty

As at 21 January 2022, there have been 57 reports of suspected ME/CFS exacerbation (relapse or flare up of symptoms) in people previously diagnosed with ME/CFS. Eighty-eight percent of reports were in females, the remaining were in males, which mirrors prevalence of ME/CFS in the general population. The average age in reporters was 48 years of age, the youngest patient was a 22-year-old female, and the oldest patient was an 80-year-old female. Two of the reports were classified as persisting disability, one was classified as requiring hospitalisation, one was classified as medically significant, and seven were classified as serious, by the reporters. All other reports were classified as non-serious.

In addition, there have been 9 reports of new onset of ME/CFS or ME/CFS-like symptoms following administration. Of these 9 reports, 3 have been reported by a healthcare professional and denote that no other viral triggers were noted prior to ME/CFS onset.

Data from international regulators and government departments on ME/CFS

There were no data identified from other regulators and government departments on the subject of ME/CFS.

Company Summary Monthly Safety Reports

Each month, Medsafe receives summary safety reports from Pfizer for the Comirnaty vaccine. Thirty-one cases of ME/CFS were identified by the sponsor during the 29 October through 15 December 2021 reporting period.

The sponsor also produced an observed versus expected (O/E) analysis of ME/CFS. The cumulative results of the analysis can be found in Table 1. O/E analyses are used to determine whether the numbers of spontaneously reported adverse events are higher than the expected background rates observed in the absence of vaccine exposure. The background incidence rates for ME/CFS were based on the incidence of ME/CFS in Olmsted County Minnesota, as estimated using the Rochester Epidemiology Project population database. [2] It is unclear from the SMSR is the cases reported are new ME/CFS cases or relapsed/exacerbated cases of ME/CFS.

The O/E ratios for both 21-day and 42-day risk windows were <1, suggesting that the number of reported cases is not higher than the expected background rate.

Table 1: Summary of O/E analysis ME/CFS in October PSUR.

Table 2. Observed to Expected (O/E) Ratios of Spontaneously Reported Adverse Events of Special Interest (AESI), Cumulative Period

	Processed Cases				All Cases[a]			
	21-Day Risk Window		42-Day Risk Window		21-Day Risk Window		42-Day Risk Window	
AESI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI	O/E Ratio	95% CI
ADEM, narrow definition	0.223	0.182, 0.271	0.159	0.130, 0.192	0.228	0.186, 0.276	0.163	0.134, 0.197
ADEM and encephalitis, broad definition	0.076	0.069, 0.085	0.057	0.051, 0.062	0.078	0.070, 0.087	0.058	0.052, 0.064
Acute kidney injury/renal failure	0.003	0.003, 0.003	0.002	0.002, 0.002	0.003	0.003, 0.003	0.002	0.002, 0.002
Acute liver injury/liver injury	0.002	0.002, 0.003	0.002	0.001, 0.002	0.002	0.002, 0.003	0.002	0.001, 0.002
Acute myocardial infarction/myocardial infarction	0.012	0.011, 0.012	0.009	0.008, 0.009	0.012	0.012, 0.013	0.009	0.009, 0.009
Acute respiratory distress syndrome (ARDS)	0.004	0.003, 0.005	0.003	0.003, 0.004	0.004	0.003, 0.005	0.003	0.003, 0.004
Ageusia/anosmia	0.182	0.176, 0.188	0.127	0.123, 0.131	0.197	0.190, 0.203	0.137	0.133, 0.142
Appendicitis	0.004	0.004, 0.004	0.003	0.003, 0.003	0.004	0.004, 0.005	0.003	0.003, 0.003
Arrhythmia	0.004	0.004, 0.004	0.003	0.003, 0.003	0.004	0.004, 0.004	0.003	0.003, 0.003
Autoimmune thyroiditis	0.038	0.033, 0.044	0.031	0.027, 0.035	0.041	0.036, 0.047	0.033	0.029, 0.038
Behcet's syndrome	0.052	0.035, 0.076	0.035	0.023, 0.051	0.058	0.039, 0.082	0.039	0.026, 0.055
Bell's palsy	0.278	0.270, 0.285	0.210	0.205, 0.216	0.288	0.281, 0.295	0.218	0.213, 0.223
Chillblains	0.019	0.016, 0.021	0.013	0.011, 0.015	0.019	0.017, 0.022	0.013	0.012, 0.015
Chronic fatigue syndrome/ME/PVFS	0.023	0.021, 0.026	0.016	0.014, 0.018	0.024	0.022, 0.028	0.017	0.015, 0.019
Coronary artery disease	0.001	0.001, 0.001	0.000	0.000, 0.001	0.001	0.001, 0.001	0.001	0.000, 0.001
Cutaneous vasculitis	0.037	0.032, 0.042	0.027	0.023, 0.030	0.038	0.033, 0.044	0.028	0.024, 0.032
Death	0.010	0.010, 0.010	0.007	0.007, 0.007	0.010	0.010, 0.011	0.007	0.007, 0.007
Deep vein thrombosis	0.059	0.057, 0.061	0.046	0.045, 0.048	0.061	0.059, 0.063	0.048	0.046, 0.050
Disseminated intravascular coagulation	0.119	0.093, 0.150	0.085	0.067, 0.106	0.119	0.093, 0.150	0.085	0.067, 0.106
Erythema multiforme	0.042	0.037, 0.047	0.030	0.026, 0.033	0.043	0.038, 0.049	0.031	0.027, 0.034
Fibromyalgia	0.001	0.001, 0.001	0.001	0.001, 0.001	0.001	0.001, 0.001	0.001	0.001, 0.001

Review of available information:

There is limited literature examining the exacerbation or onset of ME/CFS following vaccination with Comirnaty. Anecdotal evidence and surveys regarding the matter have circulated somewhat widely among the general public but are not peer-reviewed or published in scientific journals.

ANZMES Survey [3]

ANZMES conducted a survey at the request of the New Zealand ME/CFS community, to measure the effects of ME/CFS patients following their Comirnaty vaccinations.

Within the survey 191 vaccinated respondents answered a question regarding their ME/CFS status post vaccination. 70 reported a temporary worsening of their symptoms, 48 reported worsening of their symptoms in a relapse, and 8 reported worsening their symptoms beyond anything previously experienced. Moreover, 43 reported no change and 20 reported an improvement in symptoms. Cumulatively this means that 66% of respondents reported a worsening of symptoms.

The survey also asked a question about the state of general illness/wellness in ME/CFS patients following Comirnaty vaccination. reports that out of 395 respondents with ME/CFS and 144 with fibromyalgia (comorbid with ME/CFS in an unspecified number of cases), 3.1% reported a significant worsening of their symptoms, 19.8% reported a worsening of symptoms yet to return to baseline, and 32.9 reported a worsening of symptoms followed by a return to baseline. Additionally, 6.1% reported an improvement in symptoms and 38.1% reported no change. Cumulatively, 54.8% of reporters reported a worsening of their general state of illness/wellness.

Literature:

Vaccination has been suggested as being involved in the aetiology of ME/CFS. Literature examining the risk of ME/CFS exacerbation following vaccination with Comirnaty or other vaccines was not found. In addition, despite the lack of a universally accepted definition of long-COVID, there is significant interest in the potential of post-COVID-19 or long-COVID syndrome fitting under the definition of ME/CFS. A systematic review and meta-analysis that examined the long-term effects of COVID-19 has been included in the literature review for completeness.

HPV vaccination and risk of chronic fatigue syndrome/myalgic encephalomyelitis: A nationwide register-based study from Norway. (2017). [4]

An observational study conducted in the mass vaccination of Norway following the administration of the HPV Gardasil vaccine to 10–17-year-old girls throughout the six years following the vaccination programme being made available. The study identified that the incidence rate ratio of ME/CFS in boys and girls aged 10-17 was 1.15 (respectively) person-years among the 824,133 living in Norway during the six-year period examined. Further to this, the study identified that the hazard ratio (HR) for the development of ME/CFS in girls following vaccination was 0.86 during the follow-up period and 0.94 for the duration of a two-year follow up. As a result, the researchers conclude that vaccination with Gardasil did not increase the risk of ME/CFS. The study utilised the Norwegian national immunisation database and population and patient registries.

Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is associated with pandemic influenza infection, but not with an adjuvanted pandemic influenza vaccine. (2015). [5]

An observational study conducted in Norway following mass vaccinations in response to the 2009 influenza A (H1N1) pandemic, investigated the risk of ME/CFS after infection and vaccination in the entire Norwegian population. The researchers utilised the Norwegian national immunisation database to estimate that the HR of ME/CFS in those who received the H1N1 vaccine (Pandemrix, with AS03 adjuvant) was 0.97. This was contrasted with the HR following infection with Influenza of 2.04. Given that the incidence rate of ME/CFS was 2.08 per 100,000 person-months, the researchers concluded that symptomatic infection, rather than antigenic stimulation, may trigger ME/CFS.

More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. (2021). [6]

A systematic review and metanalysis of 15 observational studies examining persistent symptoms following COVID-19 infection (for a period of 14 to 110 days) found that fatigue is the most common symptoms of long-COVID-19, present in 58% of people who recovered from acute SARS-Cov-2 infection. A total of 47,910 patients were included in the analysis and were 17-87 years in age. Similarities between the symptoms observed in post-COVID-19 patients and ME/CFS patients have been acknowledged widely. This study notes that key clinical characteristics of ME/CFS, such as post-exertional malaise, inadequate sleep, and incapacitating fatigue are similar to those in patients with persistent fatigue following COVID-19 disease.

EXPERT ADVICE

It is recommended that the COVID-19 Vaccine Independent Safety Monitoring Board (CV-ISMB) is updated on the currently available information about ME/CFS following vaccination with Comirnaty.

CONCLUSIONS AND PROPOSED ACTIONS

Overall, the available data does not highlight safety concerns for the development or exacerbation of ME/CFS following administration with Comirnaty. There is an absence of literature around the risk of ME/CFS exacerbation following Comirnaty therefore it is recommended that this continues to be closely monitored through routine pharmacovigilance activities.

RECOMMENDATIONS

It is recommended that:

1.	This issue is monitored through routine pharmacovigilance activities	Yes
3.	The CV-ISMB is updated on the currently available information	Yes

References

[1] NICE Guidelines, "Myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome: diagnosis and management," 2021.

[2] Vincent A., et al., "Prevalence, incidence, and classification of chronic fatigue syndrome in Olmsted County, Minnesota, as estimated using the Rochester Epidemiology Project," *Mayo Clinic Proc.,* 2021. https://doi.org/10.1016/j.mayocp.2012.08.015.

[3] ANZMES, "Associated New Zealand ME Society (ANZMES) Preliminary Survey Findings," 2021. https://anzmes.org.nz/anzmes-preliminary-survey-findings/.

[4] Feiring B., et al., "HPV vaccination and risk of chronic fatigue syndrome/myalgic encephalomyelitis: A nationwide register-based study from Norway," *Vaccine,* 2017. https://doi.org/10.1016/j.vaccine.2017.06.031.

[5] Magnus P., et al., "Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is associated with pandemic influenza infection, but not with an adjuvanted pandemic influenza vaccine," *Vaccine,* 2015. https://doi.org/10.1016/j.vaccine.2015.10.018.

[6] Lopez-Leon S., et al., "More than 50 long-term effects of COVID-19: a systematic review and meta-analysis," *Nature,* 2021. https://doi.org/10.1038/s41598-021-95565-8.

A Comparison of the risk of death between Comirnaty mRNA vaccinated and unvaccinated individuals with pre-existing heart conditions

Vadim Pletzer, NIP Data & Analytics

30/05/2022

Acknowledgments

We'd like to thank Thomas Lumley and Ralph Stewart for their continued support and their fruitful ideas which we have implemented in this analysis.

Introduction

In New Zealand the primary vaccine used against COVID-19 is Comirnaty mRNA, which has been associated with an increased risk of myocarditis (Mevorach et al. 2021). The purpose of this analysis is to identify whether individuals with pre-existing heart conditions are at an increased risk of death post-vaccination. We tackled this question using a survival analysis.

Methodology

In this study we followed two cohorts, unvaccinated and vaccinated. Our unvaccinated cohort consists of all individuals who were discharged from hospital to a home setting in 2021, and for which they had a hospitalization event that was either heart failure or heart attack (see Table 2). We followed these subjects from their latest hospital discharge date.

In the event the subject had a hospitalization date post vaccination, we followed the subject from the hospitalization date that was prior to their first vaccination date. Subjects in the unvaccinated cohort were followed until the 15th of October if they remained unvaccinated, otherwise until, the date of death or date of their first vaccination. Subjects who received their first vaccination switch to the vaccinated cohort at their first dose date. For our vaccinated cohort we began following subjects from either the date of their first or second dose. We stopped following subjects when they received their second dose or until the 15th of October, whichever date came first.

We made no distinction between doses, that is, if a subject received a second dose we would include the same person twice in the vaccinated cohort. As a result, we ended up with an unvaccinated cohort of 15,285 subjects and 1,774 unvaccinated deaths. In the vaccinated cohort we had 19,791 observations (this number includes the same people more than once since we don't distinguish between dose one and two) and 494 vaccinated deaths.

The hazard function

To identify whether there is an increased risk of death due to vaccination, we compared the hazards for each cohort. The hazard is the instantaneous rate of death at time t given that the individual survived up to time t.

$$\lambda(t) = -\frac{1}{S(t)}\frac{dS(t)}{dt} \tag{1}$$

In Equation 1, $S(t)$ is the probability to be alive at time t and is represented as:

$$S(t) = \exp\left(-\int_0^t \lambda(t^*)dt^*\right)$$

Age-adjusted time dependent survival model

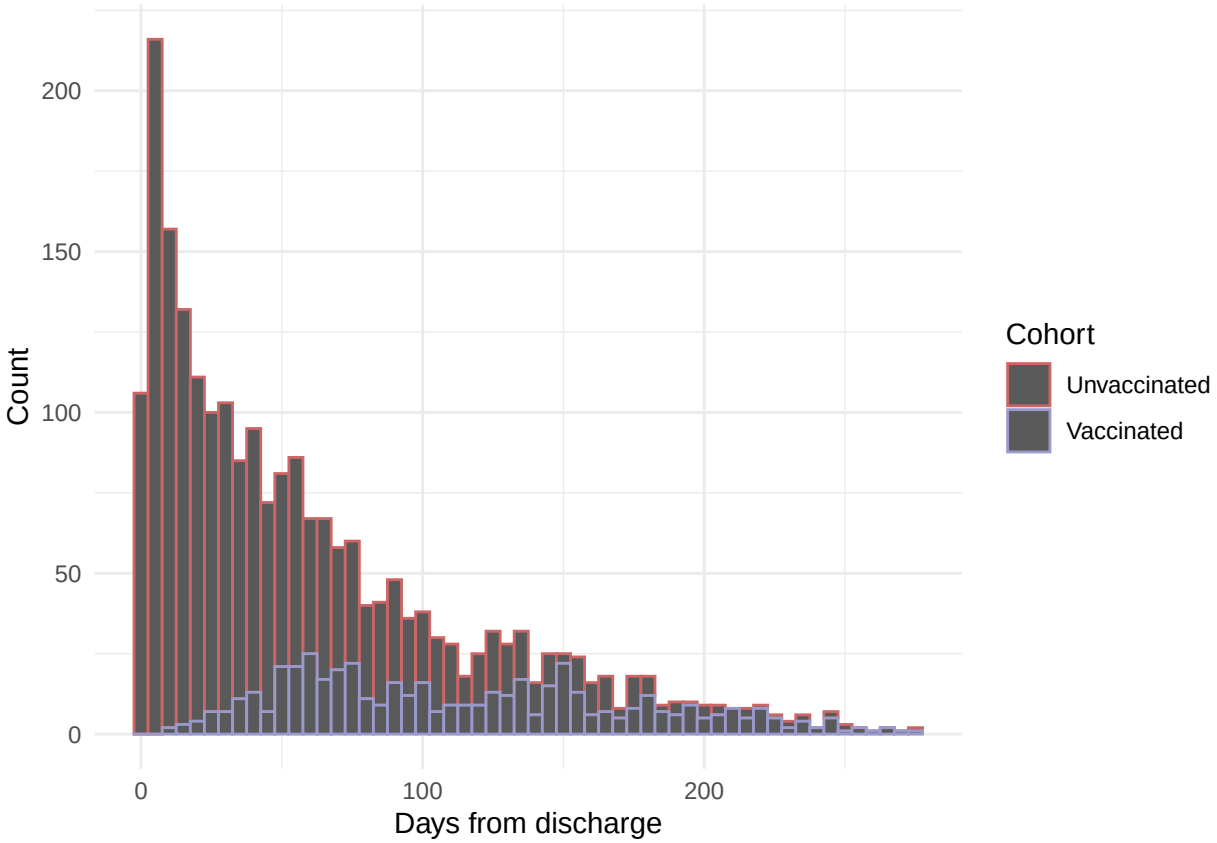


Figure 1: Distribution of days to death from date of discharge

In Figure 1, we plot the frequency of deaths following discharge for both cohorts. We observe very different distributions of death between unvaccinated and vaccinated cohorts. For the unvaccinated, most deaths occur closer to the date of hospital discharge.

In comparison, deaths among vaccinated initially increase, plateau and then decrease with the number of days since discharge. The increase and decrease are likely due to the small number of subjects being vaccinated shortly (< 50 days) and long (> 200 days) after discharge (see Figure 2).

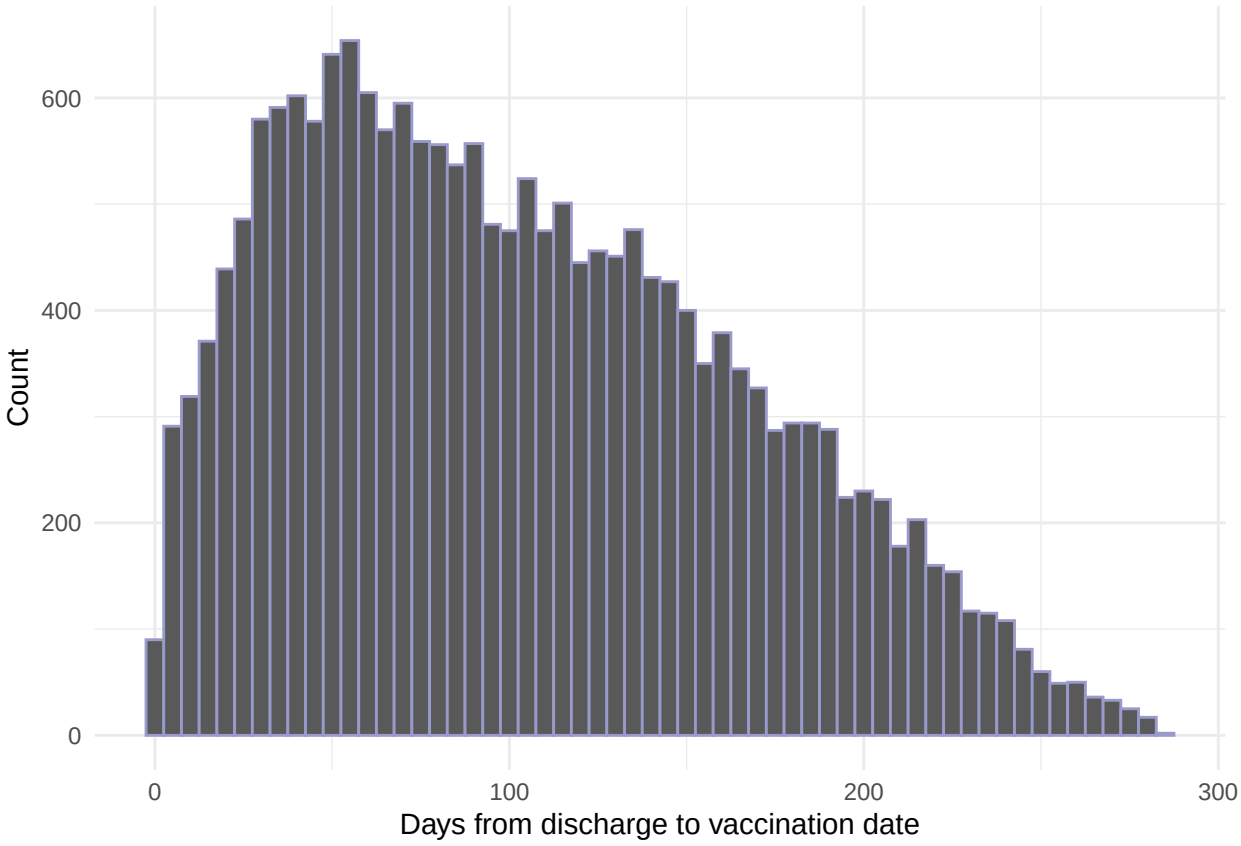


Figure 2: Distribution of days to vaccination from date of discharge

In response to these differences in the distributions of days to death, we introduce transient effects to the unvaccinated and vaccinated hazards. These effects can represent the impact of vaccination on mortality, as well as, potentially, a selection bias. A selection bias may arise if subjects with different health conditions are prioritized for vaccination.

Since mortality depends on age, we also introduce an effect for age. We model the unvaccinated and vaccinated hazards as follows:

$$\lambda_{unvaccinated} = \lambda_0(1 + a_0 \exp(-\frac{t_d}{\tau_0})) \exp(\beta z) \tag{2}$$

$$\lambda_{vaccinated} = \lambda_1(1 + a_1 \exp(-\frac{t_v}{\tau_1}) + a_2 \exp(-\frac{t_d}{\tau_0})) \exp(\beta z). \tag{3}$$

Equations 2 and 3 model the risk of death for unvaccinated and vaccinated subjects by taking into account transient effects $(1 + a \exp(-\frac{t}{\tau}))$ on the baseline hazard (λ). They also take into account the effect of age (β). The parameters to optimize are:

- $0 < \lambda_0 < \infty$, long-term hazard of unvaccinated subjects
- $0 < \lambda_1 < \infty$, long-term hazard of vaccinated subjects
- $-1 < a_0 < \infty$, selection bias among unvaccinated subjects; $a_0 > 0$ increases the hazard
- $0 < \tau_0 < \infty$, time it takes for the unvaccinated selection bias to decay
- $-1 < a_1 < \infty$, effect of vaccination on mortality; $a_1 > 0$ increases the hazard
- $0 < \tau_1 < \infty$, time it takes for the effect of vaccination on mortality to decay
- $-\infty < \beta < \infty$, effect of age on mortality; a positive β means older subjects have a higher hazard
- $-1 < a_2 < \infty$, selection bias among vaccinated subjects; $a_2 > 0$ increases the hazard.

Here, t_d is the time in days since hospital discharge, t_v is the time since vaccination for vaccinated subjects and $z = \frac{age - age_{min}}{age_{max} - age_{min}}$ is the standardized age $(0 \leq z \leq 1)$.

Results

Parameter	MLE	Lower	Upper
λ_0	8.399E-06	5.316E-06	1.148E-05
λ_1	7.585E-06	5.987E-06	9.183E-06
a_0	3.763E+00	2.368E+00	5.158E+00
τ_0	5.448E+01	3.821E+01	7.076E+01
a_1	-1.144E+00	-1.198E+00	-1.090E+00
τ_1	8.179E+00	4.121E+00	1.224E+01
β	5.745E+00	5.614E+00	5.877E+00
a_2	2.264E+00	1.326E+00	3.202E+00

Table 1: Summarizing the maximum likelihood estimates of the parameters from the age-adjusted time dependent survival model, along with lower and upper bounds corresponding to a 95% confidence interval.

After adjusting for age and transient effects, we found no statistically significant difference in the long-term hazard between the vaccinated and unvaccinated cohorts. There is no evidence that vaccination increases the risk of death among individuals with pre-existing cardiac problems.

The period following hospital discharge appears to be associated with a higher risk of mortality. In contrast, we found vaccination reduces the risk of mortality. This could indicate a strong selection bias in favour of healthy subjects being chosen for vaccination. In Figure 3, we plot the estimated hazards for the unvaccinated and vaccinated cohorts. We observe the increased hazard post-discharge and the decreased hazard post-vaccination (0, 20 and 50 days after discharge).

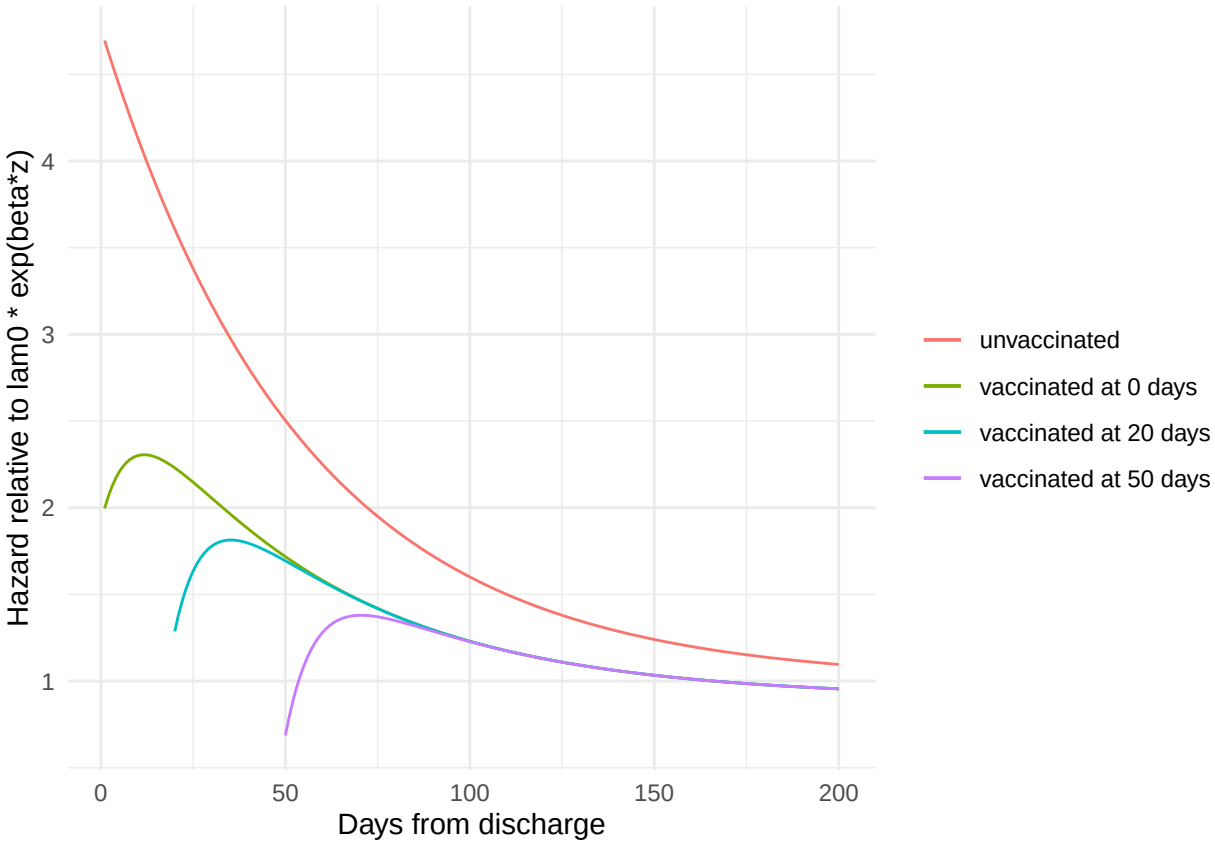


Figure 3: Hazards from days since hospital discharge

In Table 1 we summarize the maximum likelihood estimates for the parameters in the age-adjusted time dependent models (see Equations 2 and 3). We found the long-term hazards for the unvaccinated ($\hat{\lambda}_0 = 0.0000084$) and vaccinated ($\hat{\lambda}_1 = 0.0000076$) cohorts to be very close to each other. That is, among individuals who have a previous history of hospitalization for heart disease and/or heart attack, the long-term hazard (instantaneous risk of death) among those that have received at least one dose of Comirnaty is not statistically different from the long-term hazard for the unvaccinated after accounting for selection bias and age.

The transient effect on the unvaccinated ($\hat{a}_0 = 3.76$) hazard is positive. This means that for the unvaccinated, immediately after discharge, the risk of death is $1 + 3.76 = 4.76$ (see equations 2 and 3) times higher than the long-term risk of death ($\hat{\lambda}_0 = 0.0000084$). This transient effect is reduced by $\frac{1}{e}$ or 63% after $\hat{\tau}_0 = 54.48$ days. Similarly, among subjects that got vaccinated, their risk of death is also highest immediately after discharge ($\hat{a}_2 = 2.26$); the risk of death immediately after discharge is 3.26 times higher than the long-term risk of death ($\hat{\lambda}_1 = 0.0000076$). Again, this increased risk reduces by 63% after about $\hat{\tau}_0 = 54$ days. These increased risks on the unvaccinated and vaccinated hazards immediately after discharge are not statistically different.

Interestingly, the effect of vaccination reduces the hazard ($\hat{a}_1$ = -1.14). This could indicate a selection bias whereby the healthiest get vaccinated. However, this effect is short lived ($\hat{\tau}_1 = 8.18$ days).

Note that the hazard in our model can be negative immediately after vaccination, which is unphysical. This can happen when the time of discharge from hospital is larger than ≈ 130 days (see Figure 3). With more data we expect this issue to disappear.

Lastly, since we standardized age in years at start of follow-up using $\frac{age - age_{min}}{age_{max} - age_{min}}$, for every additional year in age, the risk of death increases by a factor $\exp\left(5.75/(106.475 - 0.0345)\right) = 1.056$ or 5.6%. The minimum age (age_{min}) in our data was 0.0345 years and the maximum (age_{max}) was 106.475 years.

Appendix

For each model, we maximized the likelihood of the form:

$$L = \prod_{i=1}^{N} \lambda(t_i)^{d_i} S(t_i) = \prod_{i=1}^{N} \lambda(t_i)^{d_i} \exp(-\int_0^t \lambda(t^*) dt^*)$$

and obtained maximum likelihood estimates for λ, a and τ via the *optim()* function in **R**. To ensure that the parameters fall in their range, in the likelihood function, we added a constraint whereby $\lambda(t) \geq 0$. In order to find converged maximum likelihood estimates, we used the "Nelder-Mead" method and set the maximum number of iterations to 100,000. All other arguments to *optim()* were kept as default.

In table 2 we list the ICD10 codes used to define "pre-existing heart condition." Only patients with these codes were selected for this study.

References

Mevorach, Dror, Emilia Anis, Noa Cedar, Michal Bromberg, Eric J. Haas, Eyal Nadir, Sharon Olsha-Castell, et al. 2021. "Myocarditis After BNT162b2 mRNA Vaccine Against Covid-19 in Israel." *New England Journal of Medicine* 385 (23): 2140–49. https://doi.org/10.1056/NEJMoa2109730.

ICD10 Codes
I099
I110
I260
I319
I50
I500
I501
I509
J81
R092
I21
I249

Table 2: ICD10 codes used as inclusion criteria.

Te Whatu Ora
Health New Zealand

Memorandum

To:	Dr Nick Chamberlain, National Director, National Public Health Service
From:	Dr Tim Hanlon, Group Manager Vaccine Safety Surveillance & Research, National Immunisation Programme, National Public Health Service
CC:	Rachel Mackay, Acting Director, National Immunisation Programme
Subject:	COVID-19 Vaccine Independent Safety Monitoring Board (CV-ISMB) overview
Date:	25 July 2022

Background

CV-ISMB structure and function

1. The CV-ISMB was established in February 2021 to provide expert advice around the safety of the COVID-19 vaccines to the Centre for Adverse Reactions Monitoring (CARM), Medsafe, the National Immunisation Programme (NIP) and Ministry of Health.
2. The Board has expertise from clinical medicine (including neurology, clinical pharmacology and paediatrics), general practice, microbiology and biostatistics. The Board includes members who represent the voice of Māori and Pasifika, along with a lay person to represent the interests of the consumer. Refer to Appendix 1 for current members.
3. Meetings throughout 2021 and the first half of 2022 have been held every three to four weeks. There is also the provision of extraordinary meetings, where the Board can be bought together to discuss an urgent issue.
4. Key focus areas for the Board include:
    - support with assessment of potential causal links between reported adverse events following immunisation (AEFI) and COVID-19 vaccines
    - review of 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 NIP 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 safety information for the COVID-19 vaccines.
5. The Chair and Board previously reported to the Director General of Health and NIP Steering Group respectively, however given the move of the NIP to Health New Zealand and the cessation of Steering Group it was agreed that the reporting line would move to the Interim Director, National Public Health Service in June 2022.

Current Situation

Work of the Board in 2021

6. The Board held its first meeting on 25 February 2021, with a further 15 meetings throughout 2021 (including three extraordinary meetings).
7. Eighteen safety signals for the Pfizer vaccine were considered, which led to 28 recommendations being made to either Medsafe or the Programme. Only one safety signal has been confirmed; myocarditis and pericarditis as rare adverse reactions of the Pfizer vaccine, which were added to the product label in July 2021.

8. The Board held three extraordinary meetings in 2021. The first was in April 2021 to test the process of bringing the Board together at short notice and discuss the emerging issue of thrombosis with thrombocytopenia syndrome (TTS) with the Janssen and AstraZeneca COVID-19 vaccines. The other extraordinary meetings were to discuss fatal reports where there was a sense that the Pfizer vaccine could have contributed to the events leading to the respective individuals' deaths. Further details of these meetings are provided in Appendix 2.

9. An interim report detailing the Board's work for 2021 (February-December) was produced and is published on the Ministry of Health website, along with regular meeting minutes. This information is available on the COVID-19 Who we're working with page here.

Work of the Board in 2022

10. Changes to the programme including the introduction of different COVID-19 vaccines, increased eligibility for vaccination and booster doses, require careful monitoring and messaging around safety. To date in 2022, topics considered by the Board include:

    - Use of the AstraZeneca and Novavax COVID-19 vaccines
    - Safety of booster doses in New Zealand
    - Use of the paediatric Pfizer vaccine
    - Reports of persisting disability after the Pfizer vaccine
    - COVID-19 vaccination in pregnancy

11. The Board has held one extraordinary meeting to consider two fatal reports of concern. Further details of this meeting are provided in Appendix 2.

12. The work of the Board has steadily reduced due to the decreased number of vaccine doses administered and a corresponding decrease in the number of adverse events reported (including a proportionate fall in the number of serious and fatal cases).

13. The Director, National Immunisation Programme has indicated that the Board should continue its tenure throughout 2022, due to expected programme changes (new variant vaccine and potential for infant COVID-19 vaccines).

14. The Board's tenure is agreed until 23 December 2022, with a review in September/October. The meeting cadence has been reduced to every six weeks, with the next meeting scheduled for 3 August 2022.There is still the provision for extraordinary meetings to be held at short notice, should an urgent issue arise.

Future

Future governance arrangements for vaccine safety

15. Learnings from the COVID-19 vaccine rollout should be leveraged when considering future governance arrangements for vaccine safety for the National Immunisation Programme.

16. The remit of the CV-ISMB currently only covers the safety of the COVID-19 vaccines, and the members of the Board were recruited on this basis. However, some of the expert members may wish to transition to a future vaccine governance entity.

17. The World Health Organisation (WHO) recommends that countries establish a National Immunisation Technical Advisory Group (NITAG) to guide immunisation policies and programme decisions. The importance of a NITAG was acknowledged by the Strategic Advisory Group of Experts (SAGE) on Immunisation in April 2017.

18. Broadly, the mandate of a NITAG could include the following:[1]
    - determination of optimal national immunisation policies
    - provide guidance on the development of strategies for vaccine preventable diseases through immunisation
    - advise on the monitoring of immunisation programmes, to allow the impact to be measured and quantified
    - advise the government on collection of disease and vaccine uptake information
    - guidance to organisations, institutions or government agencies around the creation of policies, plans and strategies for research and development of new vaccines and vaccine delivery technologies for the future.
19. Further work is needed to understand how the valuable work of the CV-ISMB around vaccine safety can continue in the future. The function of the CV-ISMB would preferably be designed into an existing/new group within the Ministry/Health New Zealand.
20. Ideally there will be a smooth transition between the CV-ISMB ending and a new group being stood up or an existing group taking over this function. There is a risk if that if this is not prioritised, there is a delay effecting the support available for CARM, Medsafe and the Programme.

Recommendation

It is recommended that you:

1.	note	that the COVID-19 Vaccine Safety Monitoring Board tenure has been agreed until 23 December 2022.	
2.	note	further work is needed around the future structure of vaccine safety governance.	

Signature_____ Date:

Dr Nick Chamberlain

National Director
National Immunisation Programme

[1] Duclos P. National Immunization Technical Advisory Groups (NITAGs): guidance for their establishment and strengthening. Vaccine. 2010 Apr 19;28 Suppl 1:A18-25. doi: 10.1016/j.vaccine.2010.02.027. PMID: 20412991.

Appendix 1 – Members of the COVID-19 Vaccine Independent Safety Monitoring Board (July 2022)

Name	Area of Expertise
Mr John Tait (Chair)	Obstetrics
Honorary Associate Professor Hilary Longhurst (Deputy Chair)	Immunology; Pathology
Dr Nick Cutfield	Neurology
Associate Professor Matt Doogue	Clinical Pharmacology; Endocrinology
Dr Kyle Eggleton	General Practice
Professor Chris Frampton	Biostatistics
Dr Maryann Heather	General Practice; Pacific Health
Dr Tom Hills	Immunology
Dr Wendy Hunter	Paediatrics
Professor Thomas Lumley	Biostatistics
Ms Saskia Schuitemaker	Lay person – to represent consumer interests
Dr Owen Sinclair, Te Rarawa	Paediatrics, Māori Health
Professor Lisa Stamp	Rheumatology
Dr Anja Werno	Microbiology; Pathology
Dr Enver Yousuf	General Medicine
Professor Ralph Stewart	Cardiology
Dr Laura Young	Haematology

Appendix 2 – COVID-19 Vaccine Independent Safety Monitoring Board extraordinary meetings

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, 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.

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.

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 (e.g., 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.

Two fatal reports of concern

The Board met on 2 March 2022 to consider two fatal reports of concern:

- A young person who passed away 11 days after their second dose of the Pfizer/BioNTech vaccine.
- An elderly person who passed away eight days after their booster dose of the Pfizer/BioNTech vaccine. The General Practitioner (GP) for this case had indicated that the vaccine response (fever and nausea) could have been contributory.

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

The Board discussed the case of the young person at length in December 2021, however further tests were still pending, and the Board considered this information necessary before deciding on the role of the vaccine.

The case was discussed in detail, with expert advice provided by the forensic pathologist. The case is also with the Coroner, who is investigating. Information from the post-mortem examination identified myocarditis as the most likely cause of death.

The Board considered the potential causes of myocarditis in this young person, including the Pfizer/BioNTech vaccine. The Board noted that:

- There were no reported symptoms prior to the vaccine or in the days preceding their second vaccine dose.
- This young person suffered a sudden cardiac death with no other contributing factors identified.
- The forensic pathologist described this case as having very few pathological findings but with a history that could be linked to the vaccination event.
- Children do occasionally die from sudden cardiac death; the annual incidence of sudden cardiac death in children and young adults in Aotearoa New Zealand and Australia was found to be 1.3 cases per 100,000 persons. (Bagnall et al. 2016)
- On average 95 people (SAFE study) are discharged from hospital with a principal diagnosis of myocarditis in New Zealand every year. In most of these cases the cause of myocarditis is not known but is thought to be a virus. In this individual, testing could not determine whether the vaccine was or was not the cause of the myocarditis.

Whilst it is acknowledged that some members of the Board felt that the vaccine was the probable cause of the myocarditis in this case, the majority settled on the vaccine being the possible cause of the myocarditis.

The Board considers that the circumstances of this case does not impact or change the known information on myocarditis, and the benefits of vaccination with the Pfizer vaccine for COVID-19 continue to greatly outweigh the risk of such rare side effects.

The Board noted COVID-19 infection can itself be a cause of myocarditis as well as other serious illnesses and it remains safer to be vaccinated than to be infected with the virus.

The death of the elderly person had been discussed by the Board on 9 February 2022; however, a decision on the role of the vaccine was not reached and further follow up information from the GP/Aged Residential Care facility was sought by the Centre for Adverse Reactions Monitoring (CARM).

The Director of CARM presented details of the case, with the initial report and follow up information obtained from the individual's GP. The Coroner was consulted regarding this case, however, didn't feel that the death needed to be investigated by them.

The Board considers the role of the Pfizer/BioNTech vaccine in the death of this individual unclassifiable. The Board felt 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 did not feel that the circumstances of this case changed the known safety profile of the Pfizer/BioNTech vaccine. However, reiterated that it was important for the benefit/risk for vaccination in the frail elderly to be considered on a case-by-case basis and this was reflected in the Pfizer/BioNTech vaccine data sheet.

Te Whatu Ora
Health New Zealand

Memorandum

To:	Dr Nick Chamberlain, Director National Public Health Service
Copy to:	
From:	Astrid Koornneef, Interim Director Prevention
Subject:	COVID-19 Vaccine Independent Safety Monitoring Board - Final Report and Future of the Board
Date:	19 June 2023

Purpose

1. This memo is to provide an overview of the COVID-19 Vaccine Independent Safety Monitoring Board's (the Board) final report for publication, and to provide options for the future of the Board.

Background and context

2. The Board was established in February 2021 to provide expert advice on the safety of the COVID-19 vaccines to the Centre for Adverse Reactions Monitoring (CARM), Medsafe, the National Immunisation Programme (the Programme), Te Whatu Ora, and Manatū Hauora (the Ministry of Health).
3. The Board has expertise from clinical medicine (including neurology, clinical pharmacology and paediatrics), general practice, microbiology, and biostatistics. The Board includes members who represent the voice of Māori and Pacific peoples, along with a lay person to represent the interests of the consumer.
4. Throughout 2021 and the first half of 2022, meetings were held every three to four weeks to discuss cases of note, with updates from Medsafe on safety data including signals under investigation. In the second half of 2022, the frequency of meeting was reduced to six to eight weeks. There was also the provision for ad-hoc meetings where the Board could be brought together to discuss an urgent issue.
5. The Board has continued into 2023 with an updated Terms of Reference and meetings are to take place by exception only. To date there have been no Board meetings in 2023. A final report covering the Board's work until the end of 2022 was produced and approved by National Immunisation Programme Leadership Group (PLG) on 9 May 2023. This paper seeks your approval for the publication of the final report.
6. The Terms of Reference anticipated "that the Board will continue its tenure until at least 30 June 2023 or until such time as there is a suitable alternative group available to transition the work of the Board to". This paper outlines recommendations regarding the future of the Board.

Work of the Board

7. The purpose and function of the Board is to provide expert advice on the safety of the COVID-19 vaccine(s) used in Aotearoa New Zealand. Fiji and the six Polynesian countries (the three Realm countries (Cook Islands, Niue, Tokelau), Samoa, Tonga, and Tuvalu) were offered access to Aotearoa New Zealand's vaccine portfolio and safety monitoring.
8. The pool of 12 experts across specialty areas were convened to assess potential causal links between adverse events following immunisation, review all serious or significant events, provide expert advice, and consider information about the safety of COVID-19 vaccines.

9. The expert advice from the Board was invaluable to CARM, Medsafe, and the National Immunisation Programme as part of the robust COVID-19 vaccine safety monitoring processes in place.
10. From February 2021 to November 2022, 63,999 adverse events following immunisation were reported to CARM. 3,676 of these were classified as 'serious'[1]. 784 serious cases were presented to the Board during 28 meetings held throughout 2021 and 2022 (including five extraordinary meetings).

Final report

11. The Board is required, per their Terms of Reference (Appendix 1), to provide a final report of their work. An interim report was published July 2022, covering the Board's findings from February 2021 to December 2021.
12. The focus of the Board's interim report was the Pfizer/BioNTech COVID-19 vaccine. In 2022, although the Pfizer/BioNTech COVID-19 vaccine continued to be the recommended vaccine, the programme evolved with increased use of different vaccines (AstraZeneca and Novavax), wider eligibility for booster doses and the introduction of the paediatric vaccine for 5–11-year-olds.
13. The Board has produced their final report *"Final report 2022: COVID-19 Vaccine Independent Safety Monitoring Board (CV-ISMB)"* covering the period February 2021 to November 2022 (Appendix 2). The content of the final report has been reviewed and agreed by the Secretariat, Medsafe, all the members of the Board, and the PLG. The family point of contact for the Programme has also reviewed and approved this report.
14. An overview of the safety information for the AstraZeneca, Novavax and paediatric Pfizer/BioNTech COVID-19 vaccines primary course and booster doses is provided in the final report along with an updated overview of the safety signals[2] considered for the Pfizer/BioNTech COVID-19 vaccine.
15. There have been 24 safety signals considered for the Pfizer/BioNTech vaccine which has led to 40 recommendations made by the Board to either Medsafe or the Programme.
16. Recommendations made by the Board included: suggested communications to the health sector and public; for companies to update their data sheets; and for Medsafe to continue to monitor an issue through routine pharmacovigilance activities.
17. Only one safety signal was identified in New Zealand, with myocarditis and pericarditis identified as very rare adverse reactions to the Pfizer/BioNTech COVID-19 vaccines. A safety signal for myocarditis and pericarditis was also investigated for the Novavax vaccine and an alert communication was issued after the company indicated these may be rare adverse reactions of the vaccine.
18. The Board also reviewed all reported fatal cases for the Pfizer/BioNTech COVID-19 vaccine. In cases where it was felt there could be a link between the vaccine and the event(s) leading to the fatal outcome, the Board provided a view on the probability of the association.
19. The experience and learnings from the Board are also invaluable and the report recommends that these should feed into the development of an expert immunisation advisory group to provide advice and guidance to the Programme for all vaccines in Aotearoa.

[1] An adverse event following immunisation is classified as 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.
[2] A safety signal is information on a new 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 spontaneous reports, clinical studies, and literature.

20. The full report contains no additional findings of significance from the interim report published in July 2022.

Publication

21. There has been a lot of interest in the work of the Board from both the healthcare sector and public. At the beginning of 2022, the decision was made to publish the meeting minutes for the Board and Interim Report on the Manatū Hauora website.
22. The Board's meeting minutes for 2022 were published on the Manatū Hauora website (28 March 2023). For transparency and confidence in our safety monitoring systems, it is proposed that the full final report is also published online.
23. A communications plan has been prepared to support publication (Appendix 3). This will allow for notification of key internal and external stakeholders prior to publication and provide reactive lines should there be any queries.
24. Following your approval, the attached report will also progress to the Te Whatu Ora Executive Leadership Team (ELT) (Appendix 4) and in Te Whatu Ora's Weekly Report for Ministers, for noting the intent to publish.

Future of the Board

Governance of the Immunisation System

25. In November 2022, Cabinet agreed to the establishment of a new governance mechanism for the Immunisation System [CAB-SWC-22-MIN-0227 refers[3]]. The new governance structure is an important component for the delivery of a National Immunisation Strategy and will also meet Aotearoa's obligations to provide support for the Pacific Realm.
26. The Public Health Agency within Manatū Hauora has progressed this work, with a revised structure proposed in June 2023 (Figure 1) [Health Report H2023024966 refers]. This seeks agreement from the Minister of Health to establish the Immunisation Oversight Board and the Immunisation Outcomes Collective. However, further work is required to develop the Immunisation Technical Advisory Group.
27. The Immunisation Technical Advisory Group will provide independent, evidence-based technical advice to support decision making across all aspects of immunisation and ensure that the programme is able to respond to the latest science and technical information.
28. It is anticipated that the Immunisation Technical Advisory Group will meet the requirements per the World Health Organization's Global Vaccine Action Plan (2011-2020), which called for all countries to establish or have access to a National Immunisation Technical Advisory Group (NITAG) by 2020. A NITAG is a multidisciplinary body of national experts that provide evidence-based recommendations to policymakers and immunisation programme managers[4].

[3] Cabinet Minute: Establishing Strategic Priorities for Immediate COVID-19 Vaccination and Governance for the Immunisation System
[4] Source: National Immunization Technical Advisory Groups (NITAGs) (who.int)

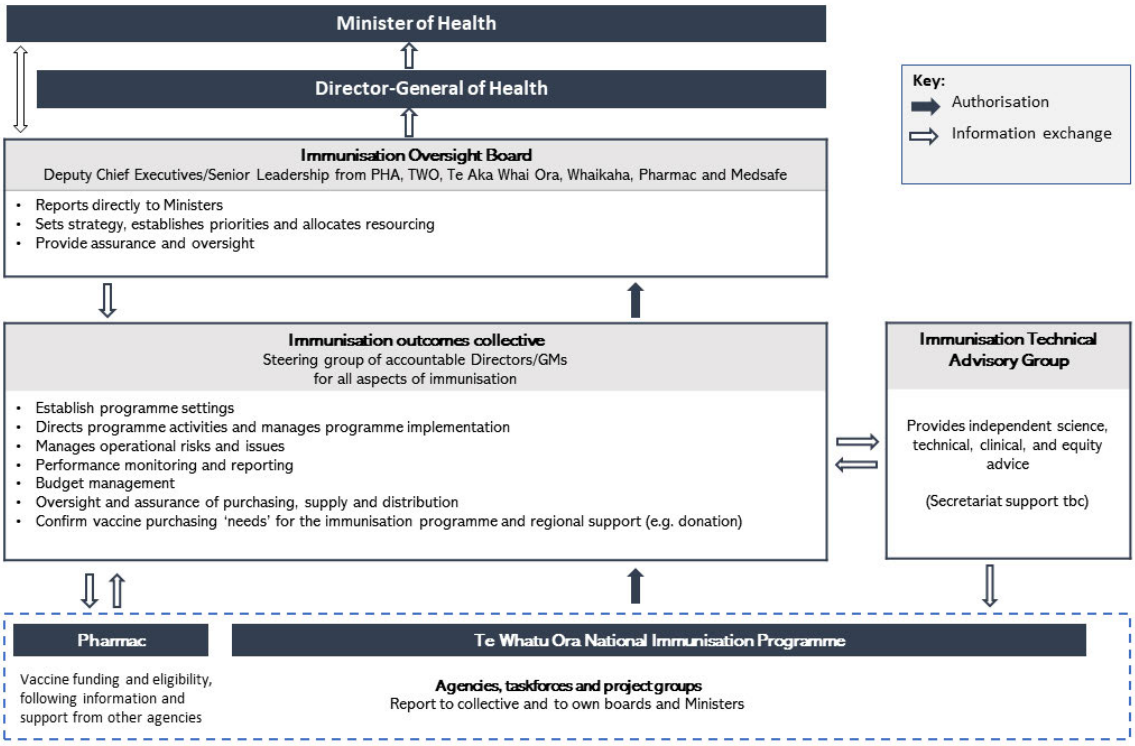


Figure 1. Revised governance structure (June 2023)[5]

29. Health agencies are working together to consider the Terms of Reference for an Immunisation Technical Advisory Group (or NITAG). In the interim, the Public Health Agency will continue to seek expert advice on issues as they emerge.

30. There is an opportunity to consider a new programme advisory group of experts to operate as the Programme's lead in the relationship with the NITAG. Further work on the requirements and establishment of this advisory group will occur following the finalisation of the NITAG Terms of Reference.

Options

31. The Board's Terms of Reference state that its tenure is until at least 30 June 2023. The Board now requires notification as to whether they are required beyond this date. In making this decision, consideration needs to be given to: the status of the COVID-19 vaccination programme; Board workload and responsibilities; business-as-usual functions; and the proposed immunisation governance structure.

32. The following options for the future of the Board have been considered:

    Option A: Discontinue the Board (recommended)

    Throughout 2021 and 2022 the Board was essential for the success and safety of the COVID-19 vaccination programme. However, with the COVID-19 vaccination programme now well-established and the final report completed, the Board has not needed to meet in 2023.

    Discontinuing the Board on 30 June 2023 will see the responsibilities of the Board return to business-as-usual processes, led by Medsafe. Medsafe would be responsible for responding to any safety signals and will refer any significant safety concerns to the Medicines Adverse Reactions Committee (MARC). This approach has been agreed with Medsafe.

[5] Health Report: H2023024966 Implementing the governance mechanism for the immunisation system

In addition, the new immunisation governance structure may present an opportunity to transfer vaccine safety responsibilities previously held by the Board, including feedback and learnings from the Board.

If this option is selected, the Board will conclude on 30 June 2023. Letters thanking the Board Chair and Board members are proposed to be sent by the Minister of Health. Draft letters are enclosed in Appendix 5.

Option B: Continue the Board (not recommended)

As an ongoing entity, with the focus on COVID-19, the current structure of the Board is not fit for purpose to support the broader National Immunisation Programme.

Selecting this option would mean the Board is extended with no change to the terms of reference, and members are to be available as needed. If any meetings are held this would incur a cost of $865 per day and $108 per hour for any part day (before tax) for Board members. With the COVID-19 vaccination programme well-established, it is not anticipated that further meetings will be required.

The Board would be disestablished at the point when the new immunisation governance structure is stood up. There is potential that this may result in duplication during the establishment phase as Board members are likely to be engaged in discussions on the new structure, and with Medsafe's responsibility for monitoring vaccine safety.

If this option is selected, this will be communicated to Board members by email.

Risks

Publication of the final report

33. The content of the report could be misinterpreted. This is mitigated by most of the information in the final report already being available in the public domain through published communications, the Medsafe Safety Report and Official Information Act (OIA) requests. The final report provides a consolidated document for information pertaining to the work of the Board.
34. If the final report is not proactively published, this will likely be requested through the OIA process. There is already a precedent with the publication of the Board's interim report. The availability of the interim report was helpful during 2022 in responding to OIAs and other queries, especially regarding potential safety signals.
35. Publication of the report could be upsetting for the families of the people who have died from a potential vaccine-mediated myocarditis, due to the level of information included. This has been mitigated through only including detail that is already within the public domain. The report was reviewed by the family point of contact within the Programme and proactive contact with the families is not needed prior to release of the report. This approach was discussed and agreed by the PLG.

Changes to the Board

36. If the Board is stood down and the new governance structure has not yet been established, there is a risk that there will be no group of experts to review any potential adverse events. As there has been no requirement for meetings in 2023, and Medsafe holds business-as-usual responsibility for this, the risk of this is low. Relevant experts may need to be reconvened by Medsafe if required.

Recommendations

It is recommended that you:

1.	Note	The report *"Final report 2022: COVID-19 Vaccine Independent Safety Monitoring Board (CV-ISMB)"* contains no additional findings of significance from the interim report published in July 2022.	
2.	Approve	The COVID-19 Vaccine Independent Safety Monitoring Board (CV-ISMB) Final Report (Appendix 2) for publication online.	Yes
3.	Approve	The attached memo (Appendix 4) for the Te Whatu Ora Executive Leadership Team (ELT) meeting on 27 June 2023 noting the intention to publish the report.	Yes
4.	Note	An update will be included in the weekly report to Ministers for noting ahead of publication of the final report.	
5.	Note	The COVID-19 Vaccine Independent Safety Monitoring Board was established in February 2021, with terms of reference through until at least 30 June 2023.	
6.	Note	The Board has been available to meet by exception in 2023. No meetings have been held to date.	
7.	Note	The Public Health Agency within Manatū Hauora is leading work to establish a new governance structure for the immunisation system, including an Immunisation Technical Advisory Group.	
8.	Note	Further work will be done to consider a new programme advisory group of experts to operate as the Programme's lead in the relationship with the NITAG.	
9.	Approve	The next step for the Board, beyond 30 June 2023: Option A: Discontinue the Board on 30 June 2023 *(recommended)* OR Option B: Continue the Board beyond 30 June 2023 *(not recommended)*	Yes No
10.	Approve	If Option A: Discontinue the Board on 30 June 2023 selected: Letters to the Board Chair and Board members thanking them for their service, to be sent from the Minister of Health.	Yes

Dr Nick Chamberlain
National Director
National Public Health Service
20 / 06 / 2023

Attachments

Appendix 1: Terms of Reference: COVID-19 Vaccine Independent Safety Monitoring Board (CV-ISMB)

Appendix 2: Final report 2022: COVID-19 Vaccine Independent Safety Monitoring Board (CV-ISMB)

Appendix 3: Communications Plan

Appendix 4: Memorandum to the Executive Leadership Team - Publication of the COVID-19 Vaccine Independent Safety Monitoring Board (CV-ISMB) final report

Appendix 5: Draft letters to the Board Chair and Board members

Difference between intradermal and subcutaneous adverse reactions following JYNNEOS vaccination

23 August 2024

Vaccine Safety
Prevention, National Public Health Service

Health New Zealand
Te Whatu Ora

Contents

Summary

Overall, the safety profile of JYNNEOS is similar between intradermal and subcutaneous administration. However, those that receive the JYNNEOS vaccine via intradermal route may experience syncope as an early onset reaction and local injection site reactions more frequently than if they were given the vaccine subcutaneously. Clinically, if the local reaction has not subsided by the time of the second dose, it is recommended to administer the second dose in the contralateral forearm. For serious adverse reactions, there is currently no evidence indicating a difference between administration routes. Regarding the vaccine in general, without considering route of administration, no new or unexpected safety signals have been identified in post-market surveillance for the JYNNEOS vaccine.

Introduction

Due to global supply constraints for the mpox vaccine JYNNEOS, alternate routes of administration have been implemented to reduce the amount of vaccine consumed per dose. The two routes for JYNNEOS are intradermal (ID) and subcutaneous (SC). For ID, a 0.1 mL dose is injected into the space between the epidermis and dermis layers of the skin. Intradermal vaccination will usually result in a small, bubble on the skin. For SC, a short needle is used to inject a 0.5 mL dose of the JYNNEOS vaccine into the subcutaneous layer and is the traditional route of administration.

The Vaccine Safety team in Prevention of the National Public Health Service has performed a rapid literature and overseas evidence review to determine if ID administration has a different safety profile from SC. Given the turnaround of less than a week, the review was not exhaustive. New Zealand based data were also collated on selected adverse events following immunisation (AEFI) that were identified from the literature review. Records of JYNNEOS vaccination in the Aotearoa Immunisation Registry (AIR) were cross-referenced with the National Minimum Dataset (NMDS) to determine the frequency of the specified AEFIs within a risk window of 42 days after vaccination. However, an extensive formal analysis was not conducted. As such, there may be additional evidence not included in this report that could impact the final conclusions.

Of note, the JYNNEOS vaccine was used in 2023 in Aotearoa New Zealand and the Vaccine Safety team conducted a Post Vaccine Symptom Check (PVSC) survey during that time. The final report did not have an analysis on route of administration. Access to the PVSC data has been archived due to migration of IT systems so we are currently unable to do an analysis retrospectively on PVSC mpox data. Additionally, only 396 survey responses were received across the entirety of the campaign (combined responses for day 7, 14, and 42 surveys) out of 4,782 vaccination events. No safety concerns were identified in the 2023 PVSC campaign.

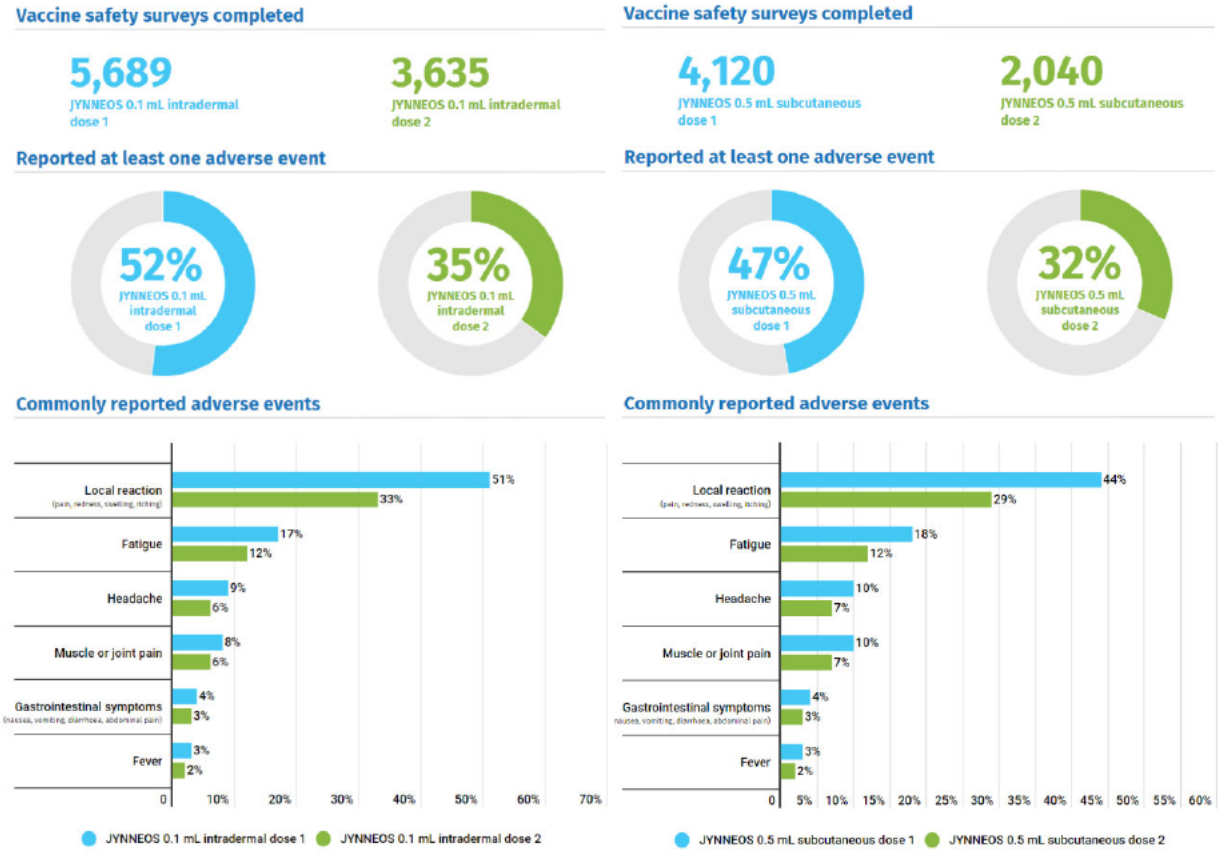
Results

Australia

Australia's AusVaxSafety, their SMS-based active surveillance programme (equivalent to PVSC), sent surveys in 2022 and 2023 to individuals who received a JYNNEOS vaccine.[1, 2] The surveys were sent 7 days after vaccination. Individuals who received JYNNEOS 0.1 mL intradermally reported slightly higher frequency of reactions (52%) than those who received the JYNNEOS 0.5 mL subcutaneously (47%), as shown in Figure 1 (ID) and Figure 2 (SC). This slight difference was driven primarily by reports of local reactions to ID, 51% compared to 44% for SC. Other commonly reported reactions were similar.

Figure 1 (left): Screen capture from AusVaxSafety on 20 August 2024. Survey results for all individuals who received a JYNNEOS mpox vaccine administered via intradermal injection and completed an AusVaxSafety survey sent on day 7 after vaccination

Figure 2 (right): Screen capture from AusVaxSafety on 20 August 2024. Survey results for all individuals who received a JYNNEOS mpox vaccine administered via subcutaneous injection and completed an AusVaxSafety survey sent on day 7 after vaccination



United States

The United States uses Vaccine Adverse Event Reporting System (VAERS) as a national passive surveillance system. In an analysis of VAERS reports from 22 May 2022 through 21 October 2022, the incidence of overall AEFIs reported were similar and not statistically different for ID and SC administration, 687 and 674 reports per million doses administered, respectively (RR = 1.03; 95% CI = 0.87–1.24).[3] Injection site erythema was the most frequently reported adverse reaction for both ID and SD, 150 per million doses compared to 107 per million doses, respectively (Table 1).

Among the 10 most frequently reported AEFIs between the two routes of administration, there were 43 reports (86 per million doses) of syncope for ID. Syncope was not listed as a top ten AEFI for SC, with pyrexia having the fewest number of reports at 23 (68 per million doses). Similarly, urticaria (120 per million) and loss of consciousness (82 per million) were reported following ID administration but were not a top 10 AEFI for SC. Pain, headache, and fatigue all appeared in the list of top 10 AEFIs by SC but not ID. Serious adverse reactions

were not stratified by administration route but there were no concerns with the overall safety profile and the CDC did not identify any new or unexpected safety signals.

Table 1: The 10 most frequently reported adverse reactions following JYNNEOS vaccine receipt, by route of administration via Vaccine Adverse Event Reporting System, United States, May 22–October 21, 2022 (reproduced directly from the publication[3])

Intradermal (n=325)			Subcutaneous (n = 212)		
Adverse reaction	**N**	**Incidence (95% CI)**	**Adverse reaction**	**N**	**Incidence (95% CI)**
Injection site erythema	75	150 (118–188)	Injection site erythema	36	107 (75–148)
Dizziness	66	132 (102–168)	Injection site swelling	36	107 (75–148)
Urticaria	60	120 (91–154)	Injection site pain	34	101 (70–141)
Injection site swelling	51	102 (76–134)	Pain	29	86 (57–123)
Syncope	43	86 (62–116)	Erythema	28	83 (55–120)
Erythema	42	84 (60–113)	Dizziness	27	80 (53–116)
Loss of consciousness	41	82 (59–111)	Headache	26	77 (50–113)
Injection site pruritus	40	80 (57–109)	Fatigue	25	74 (48–109)
Hyperhidrosis	38	76 (54–104)	Injection site pruritus	23	68 (43–102)
Pruritus	33	66 (45–92)	Pyrexia	23	68 (43–102)

Incidence = reports per million doses

Rapid literature review

Pubmed was search with the following query:

jynneos and (intradermal and subcutaneous) and (safety or adverse or reactions)

A total of 21 articles were returned. Of these, two were relevant to vaccine safety, mode of administration, used JYNNEOS in the study, and published in the last 10 years.[4, 5] A third publication had overlapping data from the United States information presented above and thus was excluded here.[6]

Out of 9,500 vaccinations at a mass vaccination clinic in Sydney, Australia, 11 (0.1%) AEFIs were recorded, all among ID vaccinations. Eight out of the 11 AEFIs were syncope, two were injection site reactions, and one mild throat itching.[4]

In a review of the Bavarian Nordic's global safety database, 'general disorders and administration site conditions' (i.e., local injection site reactions) occurred more frequently in ID (690/2732, 25.3%) compared to SC (592/2732, 21.7%).[5] Statistical significance was not calculated by the authors. The authors noted a substantial increase of syncope in ID (70/89, 78.7%) compared to SC (15/89, 16.9%).

New Zealand based data from Vaccine Safety

Based on records pulled from AIR, there were 4,782 doses of JYNNEOS given in New Zealand from 17 January 2023 through 20 August 2024 where the route of administration was known. Of these, 2,045 (42.5%) were administered ID and the remaining 2,737 (57.2%) by SC. Immunisation records were cross-referenced with the NMDS, investigating if any cases of cellulitis, sepsis, myocarditis/pericarditis, allergic reaction (acute bronchospasms, anaphylaxis, and urticaria), and syncope were coded in NMDS within 42 days following JYNNEOS vaccination. There were no events coded in the NMDS for cellulitis, acute bronchospasms, anaphylaxis, and urticaria. There was one event of sepsis, one event of pericarditis, and one event of syncope. For all events of sepsis, pericarditis, and syncope, the route of administration was ID. Given the small sample size and low frequency of events, tests of associations or effect of administration route cannot be conducted.

Conclusions

Overall, the safety profile of JYNNEOS is similar between intradermal and subcutaneous administration. However, those that receive the JYNNEOS vaccine via intradermal route may experience syncope as an early onset reaction and local injection site reactions more frequently than if given subcutaneously. Clinically, if the local reaction has not subsided by the time of the second dose, it is recommended to administer the second dose in the contralateral forearm. For serious adverse reactions, there is currently no evidence indicating a difference between administration routes. Regarding the vaccine in general, without considering route of administration, no new or unexpected safety signals have been identified in post-market surveillance for the JYNNEOS vaccine.

The Vaccine Safety team in Prevention technically has the ability to deploy another PVSC campaign for mpox. However, due to constraints in digital capabilities as of August 2024, it is not feasible in an outbreak and emergency response situation. Deployment for new PVSC campaigns need a lead time of at least three months in addition to development costs. As such, new campaigns outside of influenza and COVID-19 are not currently being considered. Active surveillance via the hospitalisation dataset can be operationalised quickly within Vaccine Safety and requires no outside resourcing. Given JYNNEOS is a novel vaccine for New Zealand, being introduced in the last two years to a population that has never received the vaccine, it is important to actively monitor the safety of the vaccine for serious AEFIs.

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Time to onset and characteristics of Brighton level 1–2 anaphylaxis following COVID-19 vaccination in Aotearoa New Zealand: Implications for post-vaccination wait times

Vaccine Safety
National Public Health Service
Health New Zealand | Te Whatu Ora
(Dated: 15th July 2025)

Contents

I. INTRODUCTION

Post-vaccination wait times are intended to monitor for and promptly respond to serious immediate adverse events following immunisation (AEFI). The main serious AEFI of concern are anaphylaxis, syncope, and convulsions.

Anaphylaxis is a severe allergic reaction that can be fatal if not treated immediately, typically with intramuscular adrenaline. Syncope (fainting) is often related to anxiety or pain and may occasionally present with convulsive movements, leading to diagnostic confusion with seizures. Importantly, convulsions may also occur during an anaphylactic episode, potentially due to cerebral hypoperfusion from vasovagal mechanisms or hypoxia. Convulsions and syncope can lead to subsequent serious injuries, particularly if driving or operating machinery.

These AEFI vary in frequency. Syncope is the most common, with rates increasing from 15 to 99 per 100,000 vaccinations depending on the number of vaccines co-administered [4]. Convulsions are less frequent. In Australia, syncopal seizures after HPV vaccination occurred at 2.6 per 100,000 doses [2]. Anaphylaxis is rare, with Brighton Criteria levels 1–2 rates for non-COVID vaccines generally low—approximately 1.3 per million doses for influenza, 0.6 for MMR, and 0.1 for tetanus toxoid vaccines [5]. In contrast, COVID-19 mRNA vaccines show a higher rate of 11.1 per million doses [6]. This may be due to unique components like polyethylene glycol (PEG), enhanced surveillance during the pandemic, novel immune responses, and early vaccination of immunocompromised or high-risk groups with different baseline risk profiles compared to routine pediatric populations.

In Aotearoa New Zealand, post-vaccination wait times differ by vaccine type. For most National Immunisation Schedule (NIS) vaccines, a 20-minute observation period is recommended. For influenza vaccines, this may be reduced to 5 minutes in certain eligible individuals ($\geq$ 13 years old, no history of anaphylaxis, etc.). For COVID-19 vaccines, the standard is 15 minutes.

Inconsistent guidance complicates decisions around observation times, particularly when vaccines are co-administered.

In 2023, the National Immunisation Programme (NIP) asked the Immunisation Advisory Centre (IMAC) to review whether current wait times for NIS vaccines should be revised. In collaboration with the Centre for Adverse Reactions Monitoring (CARM), IMAC reviewed reports of anaphylaxis, convulsions, and vasovagal syncope occurring within 60 minutes of non-COVID-19 NIS vaccination [3]. The review concluded that a 15-minute wait period could be considered for NIS vaccines.

Similarly, international bodies have reviewed early-onset AEFI. The Canadian National Advisory Committee on Immunization (NACI) in 2020 recommended a 15-minute wait post-influenza vaccination, with some flexibility for low-risk individuals — specifically, a five to fifteen minute wait for those who have previously received the influenza vaccine without a history of severe allergic reactions [1]. Other countries, including the United States, Ireland, and Australia, also recommend a 15-minute wait. The UK has no specific post-vaccine wait time guidance beyond general monitoring for immediate reactions.

Reducing post-vaccination wait times could offer several benefits: increased vaccination clinic throughput, lower risk of infection from overcrowded waiting areas, and potentially improved vaccine uptake by removing wait time as a barrier to access. Furthermore, standardising post-vaccination wait times would simplify guidance for vaccinators and support consistent compliance.

The key risk of a reduced wait time is that serious AEFI may occur outside clinical settings, potentially leading to worse health outcomes and reduced confidence in vaccination.

Following international evidence and the IMAC review, we undertook additional analyses to support evidence-based recommendations for standardising post-vaccination wait times across both COVID-19 and non-COVID-19 vaccines included in New Zealand's National Immunisation Schedule (NIS).

This analysis focused specifically on anaphylaxis—the most clinically serious and time-sensitive AEFI.

II. METHODS

Reports of anaphylaxis following COVID-19 vaccination were obtained from the Centre for Adverse Reactions Monitoring (CARM), Aotearoa New Zealand's national passive surveillance system for adverse events. CARM accepts voluntary reports from both consumers and healthcare professionals, which are reviewed and validated by clinical assessors. Each report includes a narrative description and may be linked to vaccination event data through the COVID Immunisation Register (CIR). For this analysis, reports were limited to those linked to Comirnaty (Pfizer-BioNTech COVID-19 vaccine) and occurring between February 2021 and December 2022, when vaccination was available to individuals aged 12 years and older.

To focus on acute events, only reports of anaphylaxis that were validated by a clinical reviewer and assigned a Brighton level 1 or 2 rating were included. From the clinical narratives attached to each report, time-to-onset information was manually extracted by reviewing the free-text notes. When available, we recorded the earliest time to symptom onset. In cases where symptom onset time was not specified, but the time to adrenaline administration or oxygenation was recorded, this was used as a proxy for time to medical intervention. This approach resulted in two groups of time measurements:

- **Time to symptom onset** (e.g., rash, throat tightness, difficulty breathing)
- **Time to medical intervention** (e.g., administration of adrenaline or oxygen)

Demographic characteristics (age, gender, and ethnicity) were summarised for the anaphylaxis cohort. For comparison, the general vaccinated population during the same study period was summarised using CIR data.

To describe the distribution of time to onset, we fitted a Gamma distribution to each time category using maximum likelihood estimation (MLE). The Gamma distribution was parameterised by a shape parameter α and rate parameter β, with time-to-event τ defined as $\tau \sim \Gamma(\alpha, \beta)$. The mean and variance of the distribution are given by $\mu = \frac{\alpha}{\beta}$ and $\sigma^2 = \frac{\alpha}{\beta^2}$, respectively. The log-likelihood function was maximised using the `optim` function in **R** (version 4.4.0).

From each fitted distribution, we estimated the average time to onset and estimated cumulative percentages of anaphylaxis events occurring by given time thresholds (e.g., 5, 10, 15 minutes). This analysis was performed separately for time to symptom onset and time to medical intervention.

III. RESULTS

A total of 86 validated reports of Brighton level 1 or 2 anaphylaxis following Comirnaty (Pfizer-BioNTech) vaccination were included, out of 8,172,770 doses administered between February 2021 and December 2022 (Table 1). This corresponds to a rate of approximately 1.05 anaphylaxis cases per 100,000 doses administered.

Most cases occurred in females (77 of 86; 89.5%), with a median age of 44 years. In comparison, the vaccinated population was 51% female, with a similar median age of 45 years. Among the anaphylaxis cases, 12 individuals (14.0%) had a known history of anaphylaxis, and 23 (26.7%) had a broader history of hypersensitivity. Hypersensitivity conditions included asthma, severe allergy, mast cell disorders, or related immune conditions.

Time-to-onset distributions were analysed for two outcomes: symptom onset and medical intervention. The estimated mean time to symptom onset was 15.2 minutes (95% CI: 10.1–20.4), while the mean time to medical intervention was 42.2 minutes (95% CI: 30.4–54.1).

Accumulated times are summarized in Table 2. We estimate that 25% of symptom onset occurred within 4.5 minutes, 50% by 10.6 minutes, and 75% by 21.1 minutes. For medical intervention, 25%

of cases were treated within 20.9 minutes, 50% by 35.8 minutes, and 75% by 56.7 minutes.

The Gamma distributions provided a reasonable fit to the observed data (Figure 1), capturing the timing patterns for both symptom onset and treatment events.

Table 1: Demographic characteristics of consumers experiencing anaphylaxis compared to the vaccinated cohort

Cohort	Gender, n (%)		Median age (years)	No. of reports[a]
	Female	Male		
Anaphylaxis	77 (89.5)	9 (10.5)	44	86
Vaccinated[b]	4,185,495 (51.2)	3,987,275 (48.8)	45	-

Ethnic breakdown, n (%)		
Ethnicity	Anaphylaxis cohort	Vaccinated cohort
Asian	2 (2.3)	1,299,743 (15.9)
European	60 (69.8)	5,084,820 (62.2)
MELAA	4 (4.7)	141,986 (1.7)
Maori	16 (18.6)	1,034,391 (12.7)
Other	1 (1.2)	26,720 (0.3)
Pacific Peoples	3 (3.5)	548,952 (6.7)
Unspecified	- (-)	36,158 (0.4)

History of allergy, n (%)		
Known history of anaphylaxis	12 (14.0)	–
Known history of hypersensitivity[c]	23 (26.7)	–

[a] Number of validated BC 1-2 reports following vaccination submitted to CARM.
[b] Population vaccinated with Comirnaty between February 2021 and December 2022.
[c] History of asthma, anaphylaxis, severe allergy, mast cell disorder, or related immune condition.

Table 2: Estimated and observed accumulated times by percentile for symptom onset and medical intervention

Percentile[d]	Symptom onset		Medical intervention[e]	
	Estimated (min)	Observed (min)	Estimated (min)	Observed (min)
25%	4.5	5	20.9	22
50%	10.6	12	35.8	32
75%	21.1	20	56.7	60
90%	34.9	30	81.1	80
95%	45.2	48	98.4	118
99%	69.3	61	136.7	139

[d] Percentile indicates the percentage of total accumulated reports.
[e] Medical intervention refers to the earliest reported time of treatment, such as adrenaline administration, oxygenation, etc.

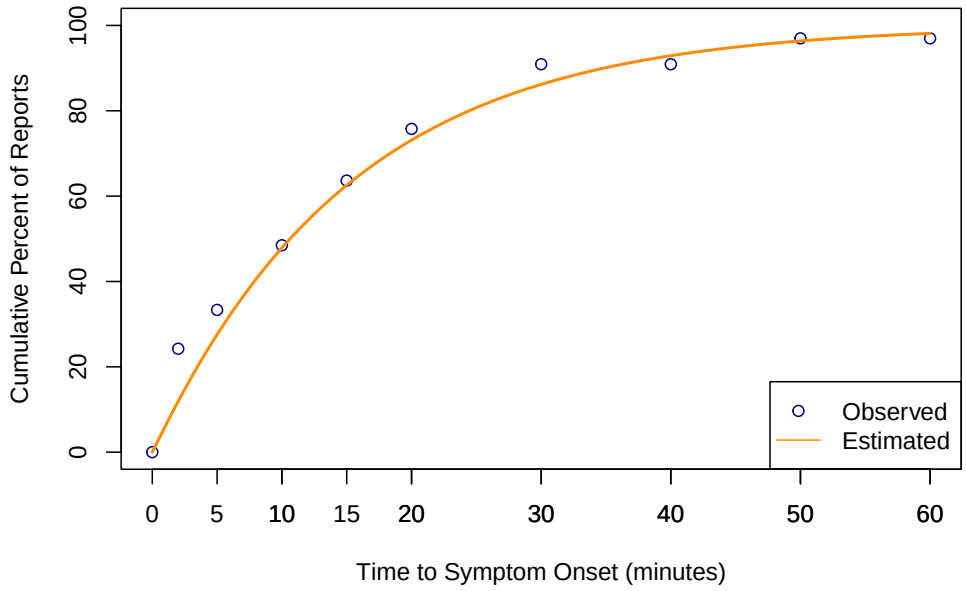
IV. DISCUSSION

Most reports were from female consumers, with a median age similar to the general vaccinated population. Anaphylaxis following exposure to LNP-mRNA vaccines, such as Comirnaty, appears to affect females more than males. This may be linked to polyethylene glycol (PEG), a lipid conjugate in these vaccines suspected to trigger anaphylaxis. Female predominance is possibly related to greater exposure to PEG-containing products like cosmetics [7]. In addition, about one third of anaphylaxis cases had a documented history of hypersensitivity, including asthma, severe allergies, mast cell disorders, or related immune conditions.

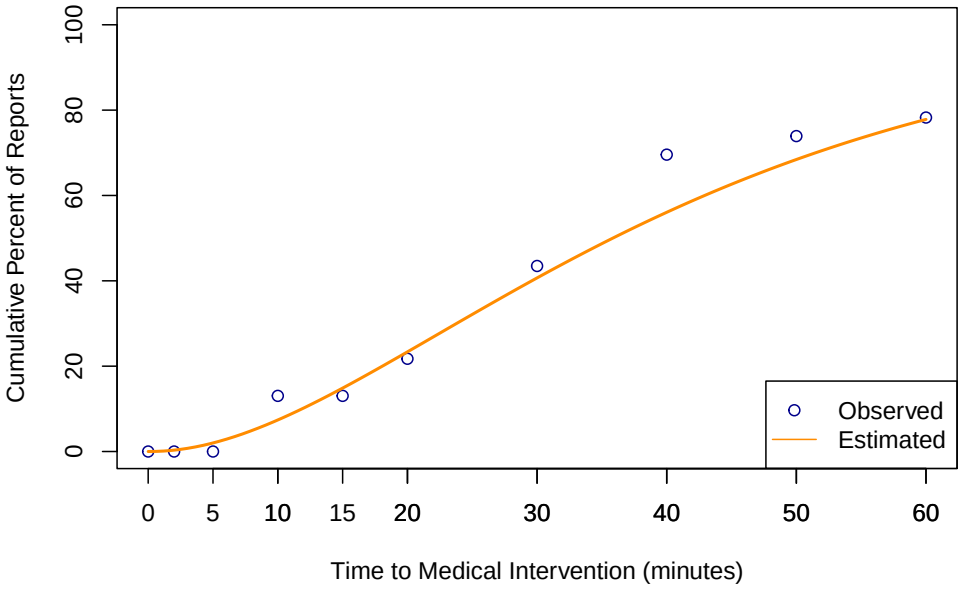
Anaphylaxis rates classified as Brighton Criteria (BC) levels 1–2 following non-COVID vaccines are generally low—for example, approximately 1.3 per million doses for influenza, 0.6 per million for

Figure 1: Observed time to occurrence (blue circles) and estimated cumulative gamma density function (orange line) for symptom onset (a) and medical intervention (b).

(a) Symptom Onset



(b) Medical Intervention



MMR, and 0.1 per million for tetanus toxoid [5]. In contrast, our study found a BC 1–2 anaphylaxis rate of 10.5 per million doses for Comirnaty, consistent with published COVID-19 mRNA vaccine rates around 11.1 per million [6]. The higher rate may reflect differences in vaccine composition, vaccinated populations (adults versus children), and heightened reporting during the pandemic. Given this rate, approximately 95,000 individuals would need to be observed to detect a single case of anaphylaxis in the observation period, highlighting the rarity of the event and the importance of balancing safety with operational efficiency.

The mean time to symptom onset was 15.2 minutes (95% CI: 10.1–20.4), while medical intervention occurred later, at a mean of 42.2 minutes (95% CI: 30.4–54.1). This delay reflects that symptoms can begin subtly and progressively worsen before treatment is required.

In Aotearoa, CARM and the Immunisation Advisory Centre (IMAC) audited anaphylaxis, bronchospasm, and convulsion reports occurring within 60 minutes of vaccination with New Zealand's national schedule vaccines [3]. They found 60% of events occurred within 10 minutes, 69% within 15 minutes, and 92% within 30 minutes. Our analysis of Comirnaty anaphylaxis reports shows 50% of events occurred within 11 minutes, 75% within 21 minutes, and 90% within 35 minutes. Although differences in case definitions and event types limit direct comparisons, the overall time-to-onset distribution for Comirnaty is broadly similar to that for scheduled vaccines.

In relation to post-vaccination wait times, Table 4 shows that extending the observation period from 15 to 20 minutes increases the estimated capture of symptom onset events from 62.6% to 73.1%, capturing approximately 10.5% more cases.

Apart from the Brighton Criteria assignment by clinical reviewers, CARM currently does not employ a fully standardised format for reporting anaphylaxis. As a result, medical narratives vary considerably—some provide detailed timing of symptom onset, others record only the time of adrenaline administration or intervention, while some reports lack timing information altogether. Similarly, documentation of patients' allergy or hypersensitivity history is variable, which may contribute to an underestimation of individuals with prior hypersensitivity in this analysis.

In conclusion, determining optimal post-vaccination wait times requires balancing the rarity yet seriousness of early-onset adverse events with the practical need for efficient vaccine delivery. While longer wait times increase the chances of promptly identifying and managing serious reactions like anaphylaxis—potentially reducing fatalities and strengthening public confidence—shorter wait times can improve vaccination throughput, reduce time barriers, and lower infection risks in waiting areas, all critical during pandemics.

V. APPENDIX

Table 3: Estimated maximum likelihood estimates (MLEs) and mean time to occurrence (minutes) with 95% confidence intervals, for symptom onset and medical intervention

Parameter	Symptom onset	Medical intervention
$\hat{\alpha}$	1.021 (0.587, 1.455)	2.122 (0.980, 3.264)
$\hat{\beta}$	0.067 (0.031, 0.103)	0.050 (0.020, 0.081)
$\frac{\hat{\alpha}}{\hat{\beta}}$ (Mean)	15.2 (10.1, 20.4)	42.2 (30.4, 54.1)

Table 4: Observed and estimated cumulative percentages of reports by time to symptom onset

Time to Onset (min)	Observed cumulative %	Estimated cumulative %
0	0.0	0.0
2	24.2	11.9
5	33.3	27.6
10	48.5	47.9
15	63.6	62.6
20	75.8	73.1
30	90.9	86.2
40	90.9	92.9
50	97.0	96.4
60	97.0	98.1
70	100.0	99.0

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