MEDSAFE

New Zealand Medicines and Medical Devices Safety Authority

Overview of Comirnaty

Safety data: Myocarditis

Out of scope

[redacted]

s 9(2)(g)(ii) [redacted]

2021

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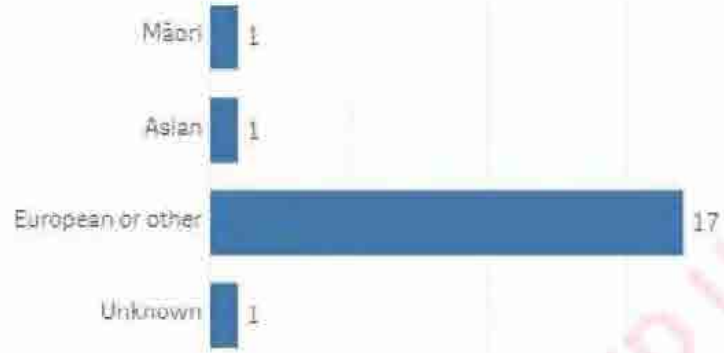
Myocarditis

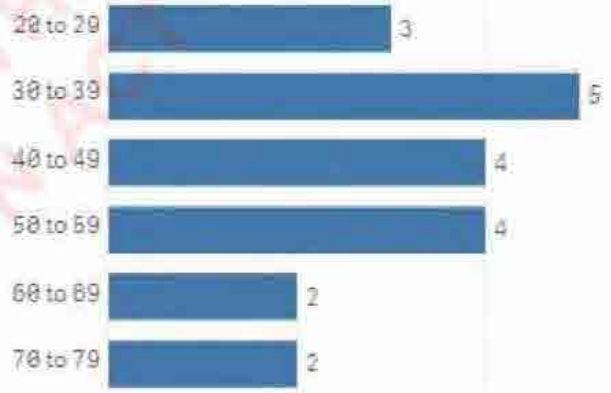
20 July – 20 cases: 9 female, 10 male, 1 unknown

reported cases



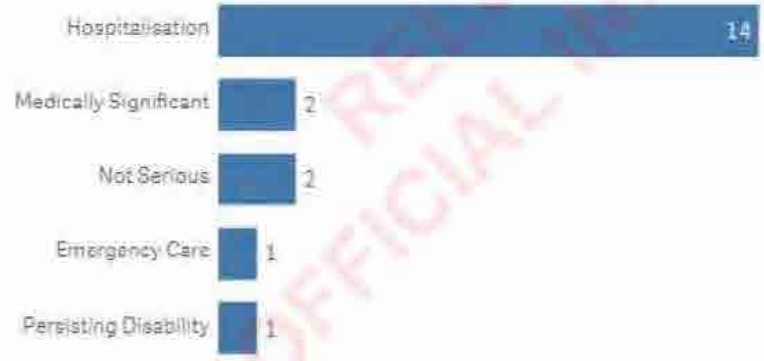
Age group at vaccination date

reported cases



Seriousness

reported cases



Outcome

reported cases

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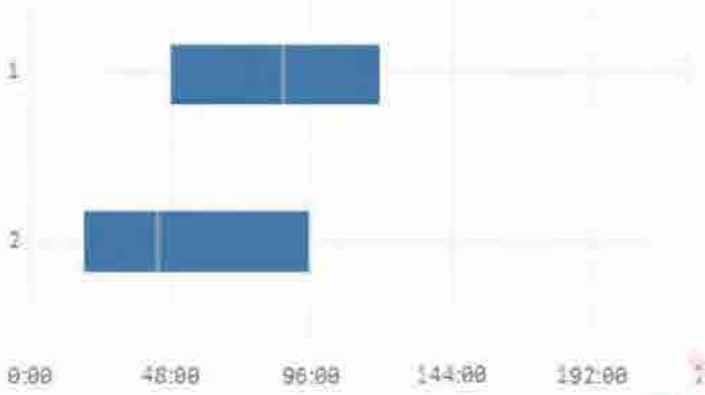
Document 1

Myocarditis

Dose number

Time to occurrence (Hours and minutes)



1 - Time to Occurrence(hh:mm)

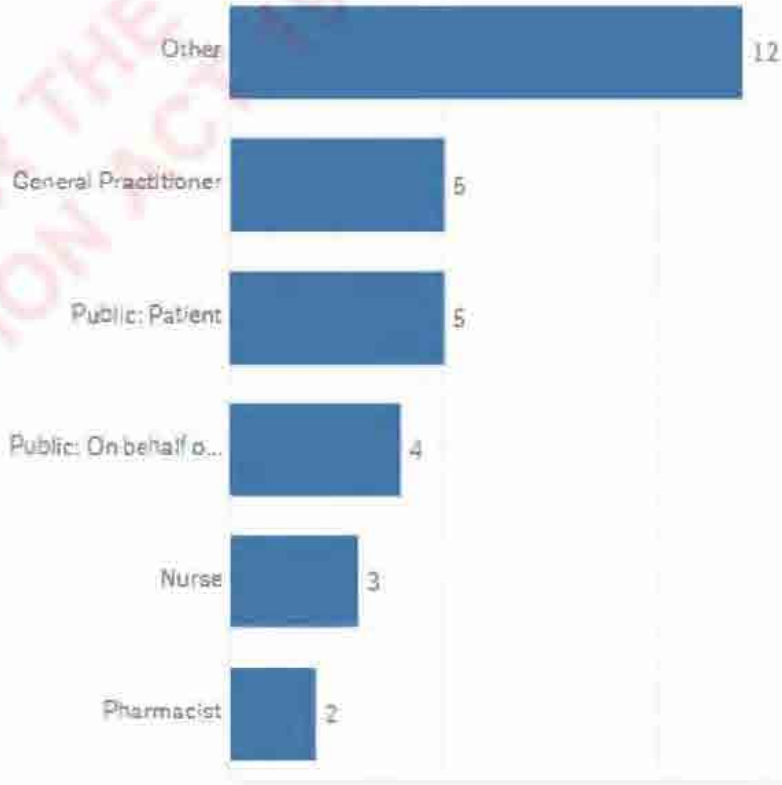
• Box end + 1.5 IQR :	225:52
• Third quartile :	119:09
• Median :	86:23
• First quartile :	48:01
• Box start - 1.5 IQR :	25:38

2 - Time to Occurrence(hh:mm)

• Box end + 1.5 IQR :	211:24
• Third quartile :	95:35
• Median :	44:24
• First quartile :	18:22
• Box start - 1.5 IQR :	5:44

Reporter type

reports



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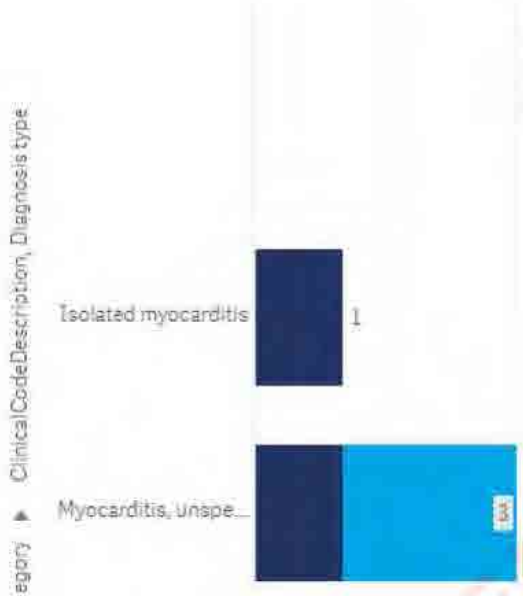
Document 1

CIR-NMDS

AESI condition

people hospitalised with AESI condition



Myocarditis - Days to admission

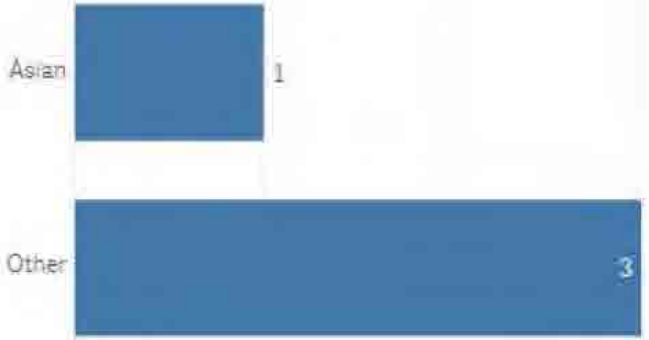
Box end + 1.5 IQR :	25.5
Third quartile :	12
Median :	4
First quartile :	3
Box start - 1.5 IQR :	1

Number of doses administered before admission

people hospitalised with AESI condition

Demographics

people hospitalised with AESI condition



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Minutes

COVID-19 Independent Safety Monitoring Board

Date:	9 August 2021
Time:	5.00 - 6.00 pm
Location:	133 Molesworth Street, Wellington & Microsoft Teams
Chair:	Mr John Tait
Attendees:	Dr Enver Yousuf, Associate Professor Matt Dooguc, Dr Hilary Longhurst, Dr Tom Hills, Professor Chris Frampton, Saskia Schuitemaker, Dr Kyle Eggleton, Professor Thomas Lumley, Dr Owen Sinclair, Professor Lisa Stamp, Professor Ralph Stewart, Dr Ian Town, Associate Professor Michael Tatley, s 9(2)(g)(ii) [redacted]
Guests:	s 9(2)(a) [redacted]
Apologies:	Dr Anja Werno, Dr Nick Cutfield, Dr Maryann Heather
Secretariat Support:	s 9(2)(g)(ii) [redacted]

Item	Notes
1	**Karakia Tīmatanga (Opening prayer)** • Dr Owen Sinclair opened the meeting with a karakia.

2	**Welcome and introduction to new CV-ISMB member and Pathologist**
	• Welcome to Professor Ralph Stewart who has joined the Board to provide cardiology expertise and s 9(2)(a) [redacted] who is the pathologist in this case
	• Outcome from this meeting is a statement from the Board noting whether:
	  ○ there is a causal link with the vaccine in this case
	  ○ we do not yet have enough information to determine if there is a causal link; details of further information required and timelines
	  ○ any communication is needed.
	• s 9(2)(g)(ii) [redacted] requested confirmation that the Board is happy for the meeting to be recorded.

3	**Case overview**

Document 2

	• s 18(c)(ii) [redacted]
4	**Case presentation** s 18(c)(ii) [redacted]

Document 2

	s 18(c)(ii) [redacted]
5	**General discussion** s 18(c)(ii) [redacted]

Document 2

s 18(c)(ii)

[redacted]

Document 2

s 18(c)(ii)

[redacted]

s 18(c)(ii) [redacted]

- Saskia was asked to comment from a consumer's point of view
    - Good for public to know about the robust process this Board goes through to review adverse events. This, as well as CV-TAG and other advisory groups, should provide the public with confidence.
    - Should be made more visible, in plain language
    - Public need education about relative risk, e.g. discussing risks of complication or death if you do not get vaccinated.
- s 9(2)(g)(i) [redacted]
- The Chair asked that the Board confirm a statement noting that the vaccine looks like the most likely cause, but that further investigations are underway.
    - Circulate statement around the Board for comment with the proviso that we are awaiting further information to come.
- It was noted the Board needed to be careful about where responsibility lies in terms of establishing cause of death since this case is with the Coroner, with more focus on the association with the vaccine.
- It was agreed that the Board could not exclude that the vaccine caused the myocarditis which led to death in this case and any messaging needed to be clear on this. However, messaging should note the vaccine remains effective and safe.
- s 9(2)(g)(i) [redacted]
- Dr Tatley noted the importance of greater awareness and management of these cases to prevent similar scenarios. s 9(2)(g)(i) [redacted]
- Messaging to reinforce the robust nature of the role of this Board and the comprehensive evaluation this case is going through currently.
- CARM often receive questions about how these cases are evaluated, so this is an opportunity to put out that sort of message as well.
- If we revisit first case of myocarditis early in the programme, that patient presented to his GP with non-specific chest discomfort, but the GP correctly referred the person to hospital. It is a difficult situation as there are a lot of reports of chest discomfort which are not myocarditis related.
- The Chair noted the Board would need to confirm messaging for the CVIP National Director and Director-General.

Document 2

	• s 9(2)(g)(ii) introduced s 9(2)(g)(ii) and two key summary points for circulating:
	  ○ statement noting advice from Board to the CVIP around messaging that this death is associated to some degree with the vaccine, and;
	  ○ other communication issues that the Board have raised. To discuss further at the upcoming in person meeting.
	• s 9(2)(g)(ii) commented that MoH would shape some options and recommendations and circulate shortly.
	• The Board Chair thanked everyone and handed to Dr Owen Sinclair to close with a karakia.

6	**Karakia whakamutunga (closing prayer)** Dr Owen Sinclair closed the meeting with a karakia.

Document 3

Comirnaty and myo/pericarditis

August 2021

Medsafe

2021

Other mechanisms ?

- Molecular mimicry between the spike protein and self-antigens - time frame and dose 1 reaction do not support that
- A delayed hypersensitivity reaction, such as serum sickness–like reaction or eosinophilic myocarditis – not supported by current data according to Bozkurt.
- Leakage of mRNA into blood – myocarditis induced in mice by iv not im administration (Li et al 2021)
- Reactions after dose 1: robust inflammation induced by the LNPs. Reactions after dose 2: similar but more robust inflammatory reaction + adaptive immune response formed after dose 1 - from mice studies (Ndeupen et al 2021).
- The SARS-CoV-2 spike glycoprotein attaches to endothelium via ACE enzyme 2 which results in complement-mediated microvascular injury where endothelia have high ACE2+ expression. The myocardium is one such place - seen in skin reactions (Magro et al 2021).
- Sex differences: The prevalence of myocarditis in young males may reflect signal potentiation by male hormones, cardio protection by female hormones or other hormone independent differences.

Myocarditis

- 12 cases, 8 females and 4 males
- 7 after dose 2 and 5 after dose 1

Age range	s 9(2)(a)
< 30	
31-40	
41-50	
51-60	

Pericarditis

- 13 cases, 6 females and 7 males
- 11 after dose 2 and 2 after dose 1

Age range	s 9(2)(a)
< 30	
31-40	
41-50	
51-60	
61-70	
71-80	

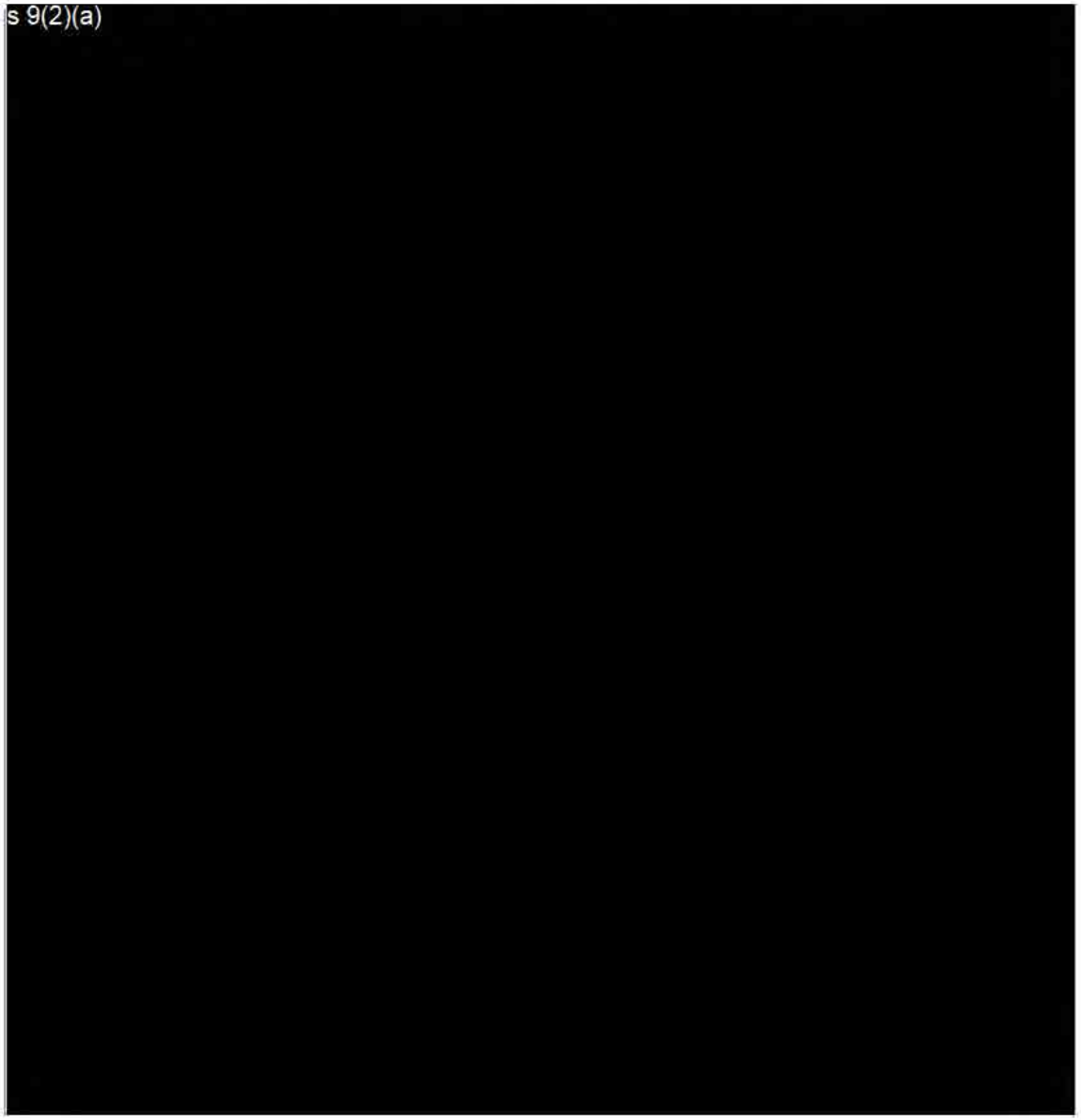
Document 3

Myocarditis/Pericarditis (CARM)

Dose 1 cases

Document 3

Dose 2 cases, Myocarditis/Pericarditis (CARM)

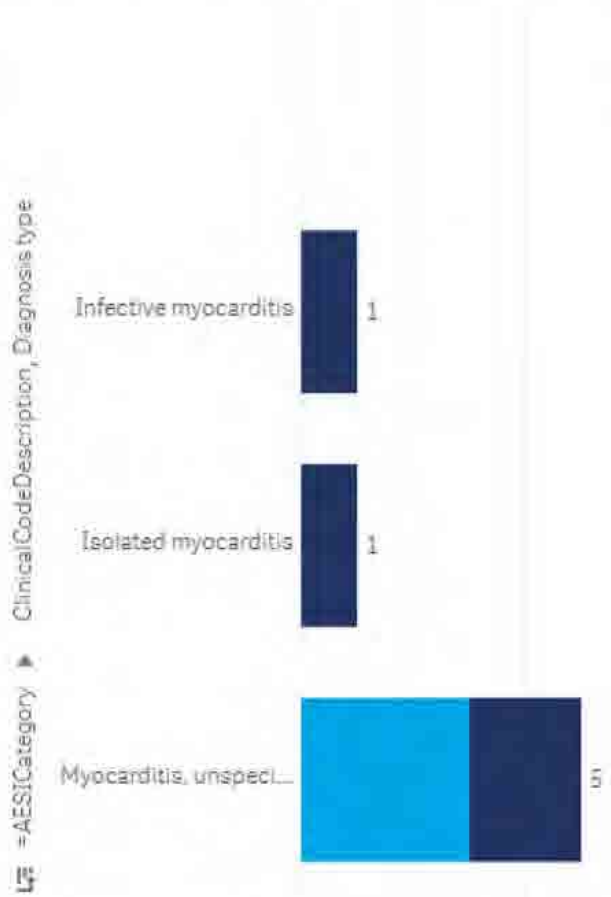


Document 3

Myocarditis – data linkage

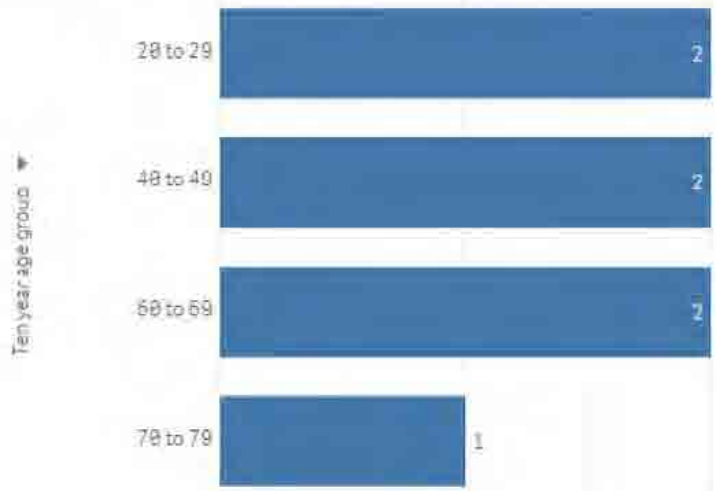
AESI condition

people hospitalised with AESI condition



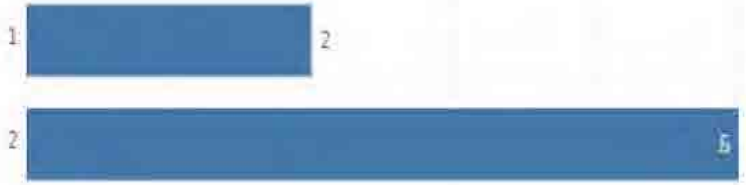
Demographics

people hospitalised with AESI condition



Number of doses administered before admission

people hospitalised with AESI condition

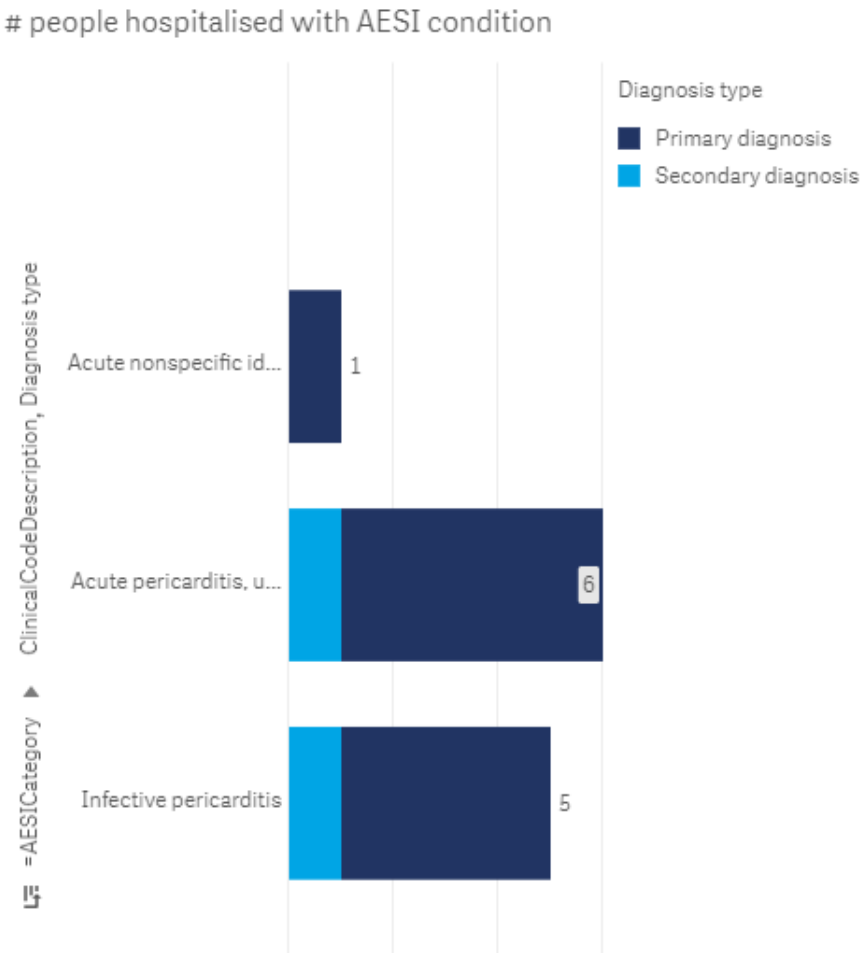


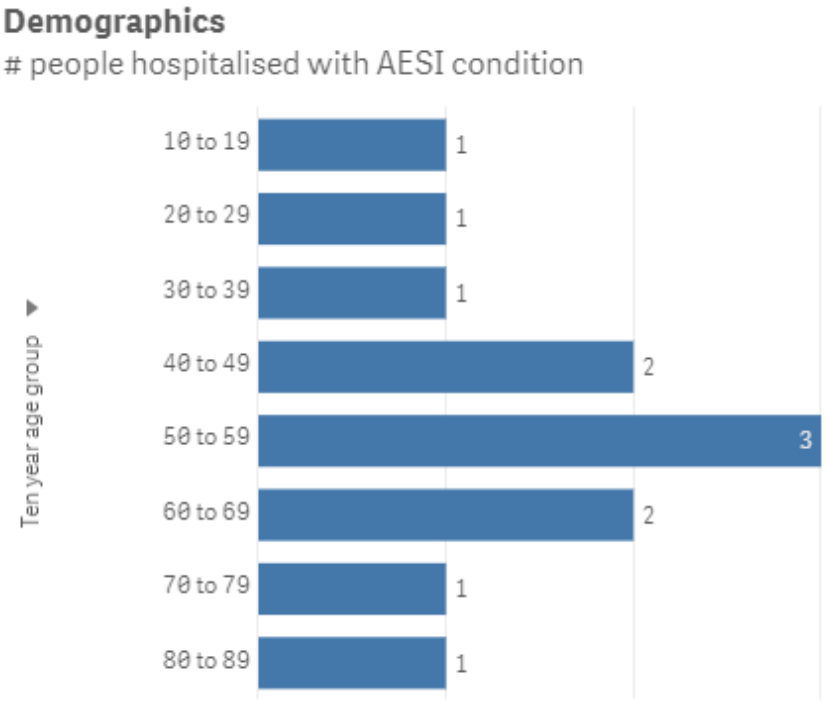
Date

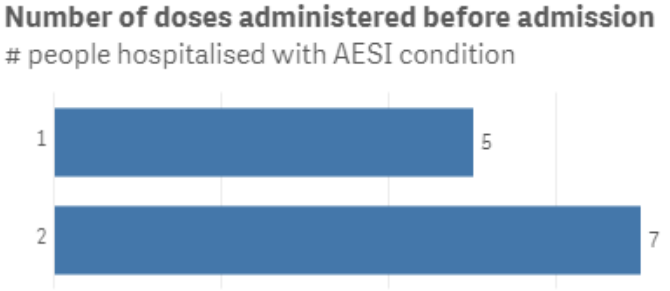
s 9(2)(g)(ii)

Document 3

Pericarditis- data linkage





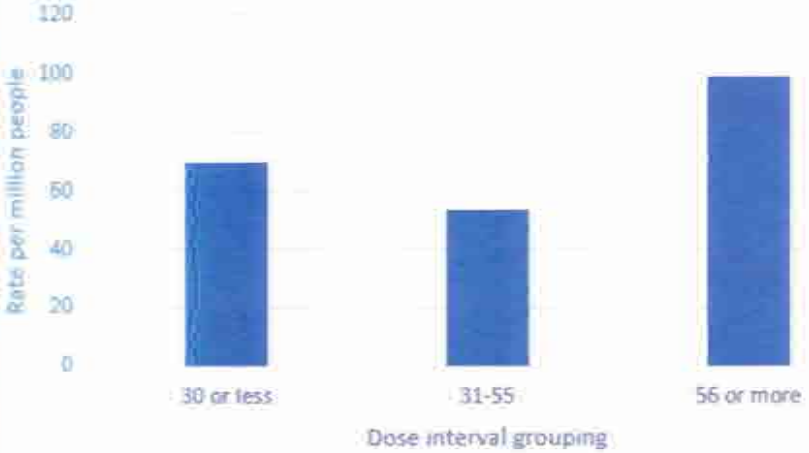


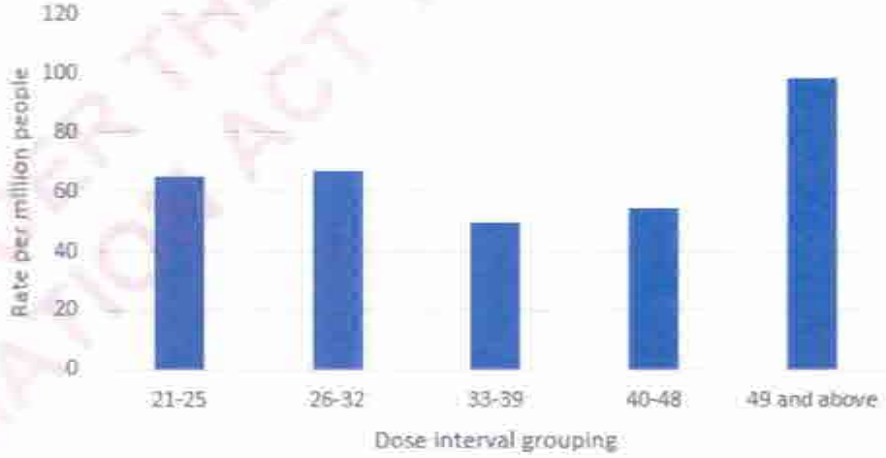
Comirnaty and myo/pericarditis

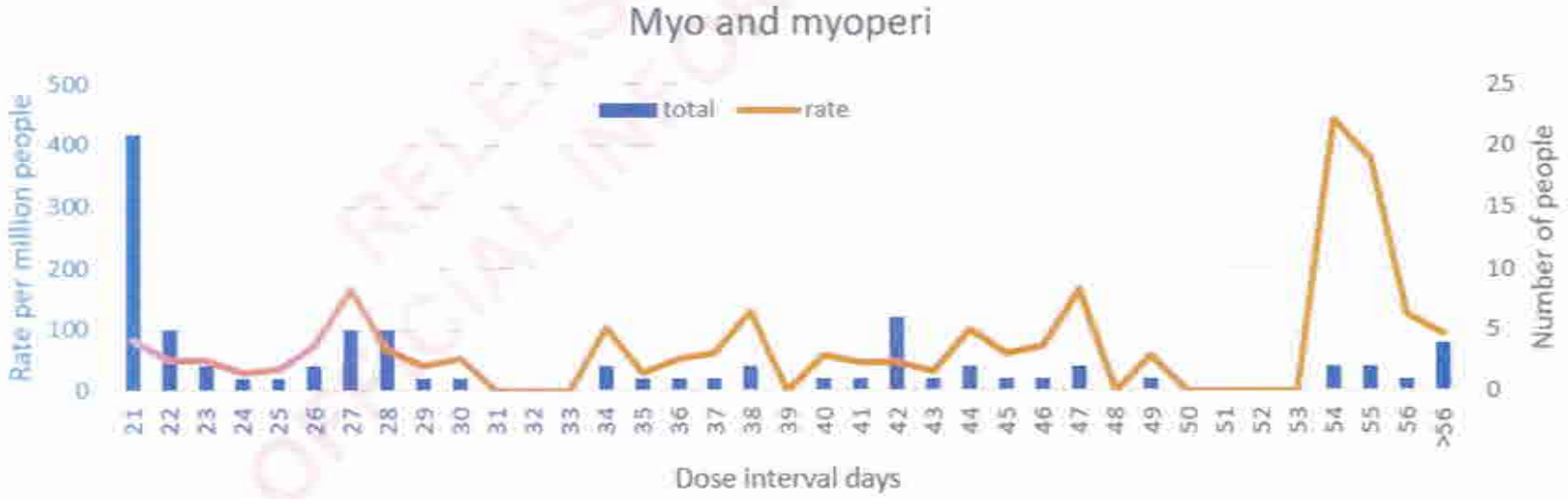
9 September

Medsafe

Dose interval- myocarditis and myopericarditis







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Document 4

Myocarditis

- 14 cases, 11 females and 3 males
- 8 after dose 2 and 6 after dose 1

Age range	s 9(2)(a)
< 30	
31-40	
41-50	
51-60	
61-70	
71-80	

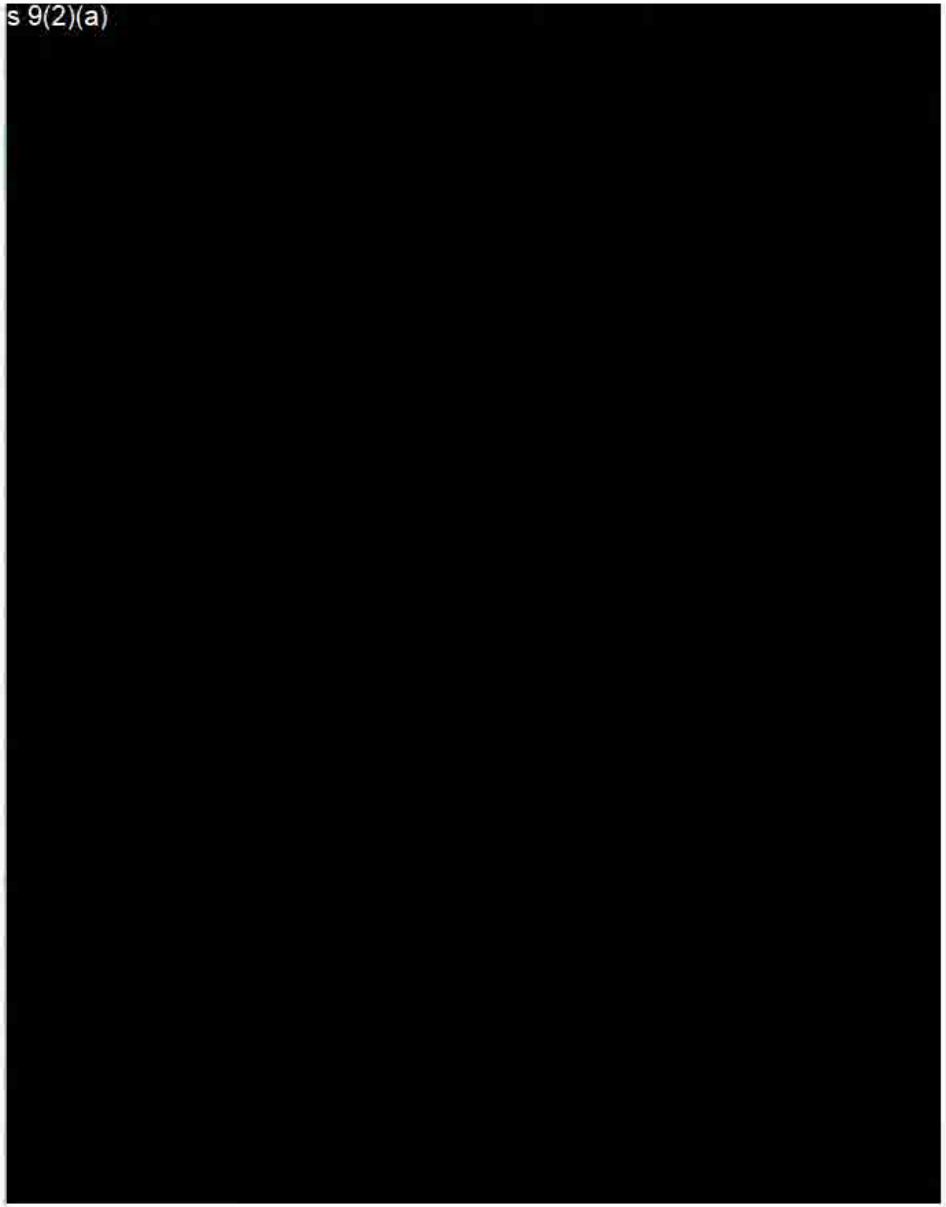
Pericarditis

- 25 cases, 12 females and 13 males
- 15 after dose 2 and 10 after dose 1

Age range	s 9(2)(a)
< 30	
31-40	
41-50	
51-60	
61-70	
71-80	

Document 4

Dose 1 cases Myocarditis/Pericarditis (CARM)



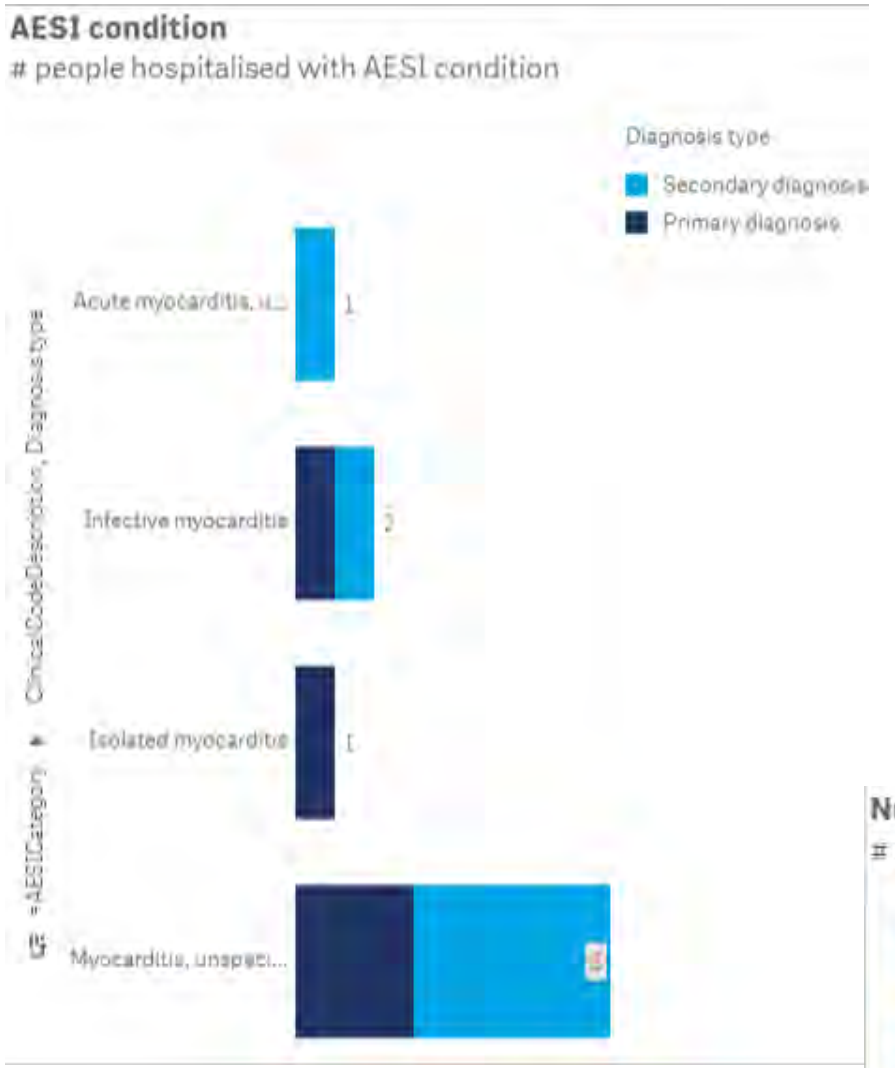
Document 4

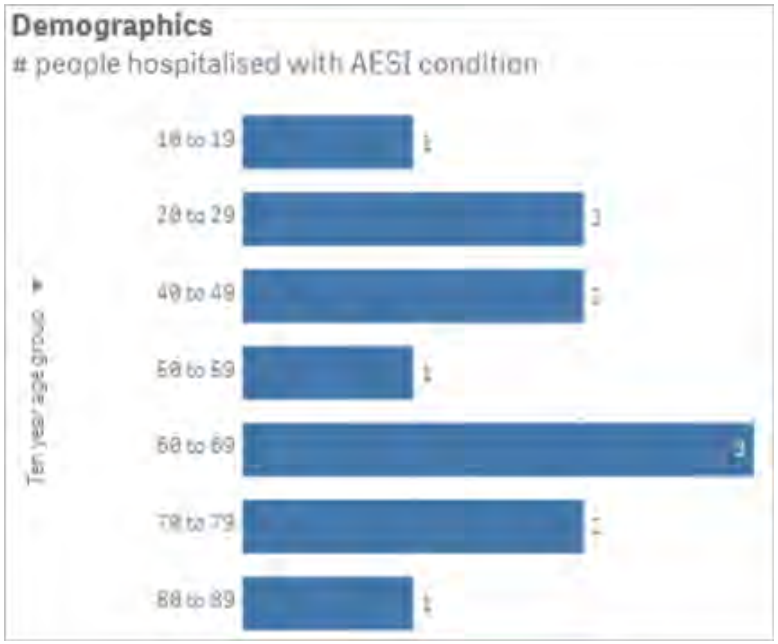
Dose 2 cases, Myocarditis/Myopericarditis (CARM)

Dose 2 cases, Pericarditis (CARM)

Document 4

Myocarditis – data linkage



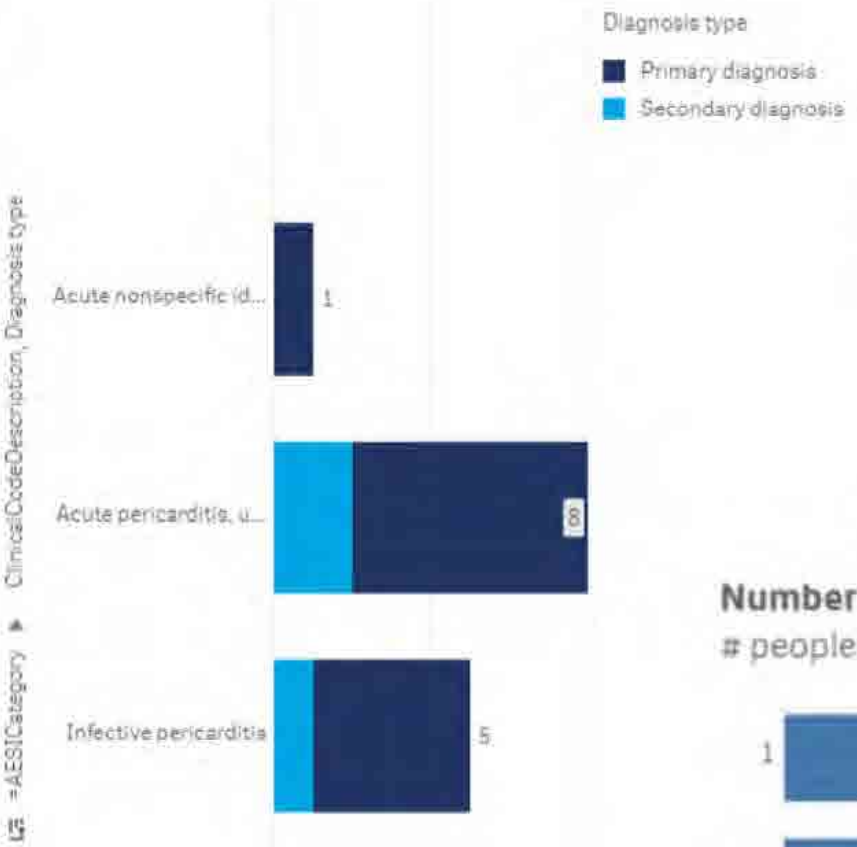


Document 4

Pericarditis- data linkage

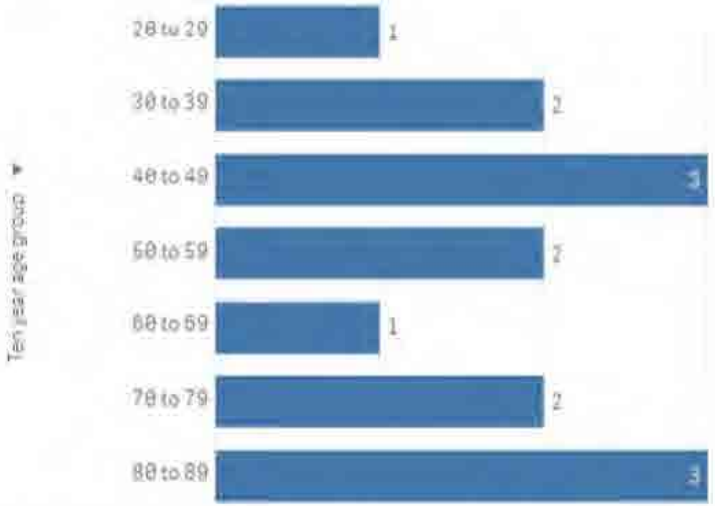
AESI condition

people hospitalised with AESI condition



Demographics

people hospitalised with AESI condition



Choose alternative dimensions such as DHB of residence, Deprivation quintile 2013, Ten year age group, Gender , Ethnic group MPAO on the left

Number of doses administered before admission

people hospitalised with AESI condition

Document 5

Memo

Date:	22 October 2021		
To:	s 9(2)(g)(ii) Manager, Clinical Risk Management, Medsafe		
From:	s 9(2)(g)(ii)		
Subject:	**Pregnancy-related AEFI reports in New Zealand following administration of Comirnaty**		
Incident ID:	28449	**Lotus Notes Location:**	Immunological Products & Vaccines - ISMB
For your:	Action: [√]	Decision: [√]	Information: [√]

DESCRIPTION

This memo reviews the cases describing pregnancy-related adverse events following immunisation (AEFIs) after administration of Comirnaty, summarises the information currently available on this issue, and considers whether any further action is required.

NATURE OF THE SAFETY CONCERN

Safety of vaccines during pregnancy

Vaccine-preventable diseases can be associated with significant morbidity and mortality in pregnant people, foetuses, and neonates. In some cases, immune system changes during pregnancy can increase the susceptibility of the pregnant person and foetus to certain infectious diseases and increase the risk of serious outcomes. Vaccination can provide direct protection of pregnant women, and can also protect the foetus and infant through placental transfer of antibodies during pregnancy [1, 2].

There are no safety concerns surrounding administration of non-live vaccines during pregnancy. Caution around administration of live attenuated vaccines such as the measles, mumps and rubella (MMR) vaccine is based on the theoretical risk of placental transfer of attenuated virus and subsequent infection of the foetus. However, evidence of foetal harm after vaccination has not been identified. A review of the evidence around safety of vaccination during pregnancy by the Global Advisory Committee on Vaccine Safety found no safety concerns with influenza, tetanus toxoid, meningococcal, MMR, poliovirus or yellow fever vaccines (Table 1) [1, 2].

Table 1: Summary of vaccines reviewed by the Global Advisory Committee on Safety and level of evidence concerning vaccine safety. Source: Global Advisory Committee on Vaccine Safety. 2014. Safety of immunization during pregnancy: a review of the evidence July 2014. URL: who.int/publications/i/item/safety-immunization-pregnancy (accessed 12 October 2021).

Vaccine	Increased risk or severity of disease in pregnant women	Risk of disease to fetus or young infant	WHO recommendation on vaccination during pregnancy	Vaccine safety concerns	Level of evidence on vaccine safety
Inactivated vaccines					
Seasonal TIV or H1N1 2009–2010 monovalent, non-adjuvanted vaccines Oil-in-water adjuvanted, monovalent H1N1 vaccines	More severe disease especially in second and third trimester and increased risk of death in a pandemic	Possible increased spontaneous abortion rate and increased preterm delivery. No malformations confirmed.	Yes Yes	No safety concern identified No safety concern identified	++++ +++
Tetanus toxoid vaccines	Incidence depends on region; unaltered by pregnancy	Neonatal tetanus mortality 60%	Yes	No safety concern identified	++
Meningococcal polysaccharide vaccines Meningococcal conjugate vaccines	Incidence not altered by pregnancy	Unknown for fetus; infants may develop significant morbidity and mortality.	No As part of mass campaigns.	No safety concern identified No safety concern identified	++ +
Live attenuated vaccines					
Rubella vaccine	Incidence not altered by pregnancy	Abortion and congenital rubella syndrome (CRS)	No	No CRS identified in children born to inadvertently vaccinated susceptible pregnant women	+++
Measles vaccines	More severe disease; low mortality	Possible higher abortion rate, infrequently congenital measles and if premature possible high case fatality rate	No	No safety concern identified	Indirect data from combined MR vaccines
Mumps vaccine	Incidence not altered by pregnancy	Probable increased rate of abortion in the first trimester	No	No safety concern identified	Indirect data from combined MMR vaccines
Oral poliovirus vaccine	Increased risk of paralytic disease	Anoxic fetal damage reported; 50% mortality in neonatal disease	No	No safety concern identified	+++
Yellow fever	Incidence not altered by pregnancy	Unknown	During epidemics and when travel to endemic areas cannot be avoided	No safety concern identified	+++

++++ Substantial evidence from RCTs, large observational studies or registries with pregnancy follow-up and passive surveillance.
+++ Evidence from observational studies or registries with pregnancy follow-up and passive surveillance.
+ + Some evidence from studies with lower power, lack of information on some relevant pregnancy outcomes, short follow-up of offspring or other limitations of study design and passive surveillance.
+ Passive surveillance data.
- No data.

Assessment of the safety of vaccination during pregnancy must be undertaken in the context of the risks associated with infection without vaccination. The evaluation of vaccine safety is complicated by the task of distinguishing the inherent risks of pregnancy from risks associated with vaccination. This requires knowledge of background rates of adverse pregnancy outcomes [1].

Clinical trials usually do not include pregnant or lactating women and newer vaccines often have limited post-market experience in pregnant women. Post-market safety studies face methodological challenges such as small sample sizes, limited detection of early pregnancy loss, and the long-term follow-up required to detect congenital effects. Despite these challenges, there is substantial evidence supporting the safety of vaccination during pregnancy [1].

Risks of COVID-19 disease during pregnancy

The World Health Organisation (WHO) COVID-19 Vaccine Safety Surveillance Manual includes the following information on the risks of COVID-19 disease during pregnancy [3]:

> 'While there is no indication that pregnant women have an increased susceptibility to infection with SARS-CoV-2, evidence suggests that pregnant women with COVID-19 are at higher risk of developing severe disease compared to non-pregnant women of reproductive age. As seen with non-pregnant women, a high proportion of pregnant women have asymptomatic SARS-CoV-2 infection and severe disease is associated with recognized medical (eg, high body-mass index, diabetes, pre-existing pulmonary or cardiac conditions) and social (eg, social deprivation, ethnicity) risk factors. Pregnant women with symptomatic COVID-19 appear to have an increased risk of intensive care unit admission, mechanical ventilation and death in comparison

with non-pregnant women of reproductive age, although the absolute risks remain low. COVID-19 may increase the risk of preterm birth, compared with pregnant women without COVID-19, although the evidence is inconclusive.

SARS-CoV-2 has been observed in the placenta and some case reports suggest that vertical transmission of the virus to infants born to infected women may occur (as opposed to postpartum infection). However, congenital COVID-19 infections have not been reported so far during the pandemic. The acute effects of the disease on neonates and infants have been secondary to complications arising from severe maternal illness and medically indicated preterm delivery or caesarean delivery due to clinician concerns.

There is no evidence that SARS-CoV-2 can be transmitted via human breast milk.'

Spontaneous abortion

Spontaneous abortion or miscarriage is a non-viable pregnancy up to 20 weeks gestation. Most commonly, this occurs during the first trimester, which is referred to as early pregnancy loss. Second trimester pregnancy loss occurs after 13 and before 20 weeks gestation and still-birth refers to pregnancy loss at 20 weeks gestation or later [4].

The true incidence of early pregnancy loss is difficult to ascertain as many losses occur before the pregnancy is clinically recognised. The incidence of spontaneous abortion is thought to be around 10% of clinically recognised pregnancies, but has been estimated to be as high as 31% of all pregnancies based on logistic regression. The risk of pregnancy loss changes with age. One study found rates of early pregnancy loss of 17 percent (<20 years), 11 percent (20 to 24 years), 10 percent (25-29 years), 11 percent (30 to 34 years), 17 percent (35 to 39 years), and 33 percent (40 to 44 years) [4].

Other risk factors for pregnancy loss include prior pregnancy loss, diabetes, obesity, thyroid disease, stress, use of certain medicines and substance use. Some infections (eg, untreated syphilis, Zika virus) have been associated with increased risk of spontaneous abortion, although the mechanism for this is unclear [4].

Chromosomal abnormalities are present in up to 70% of spontaneous abortions, but this varies by gestational age. Maternal anatomic abnormalities and significant trauma may also cause pregnancy loss. There are many factors associated with second trimester pregnancy loss, with underlying pathology overlapping with obstetric complications. There can be multiple factors involved in second trimester pregnancy loss and often no cause is identified [4].

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 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

Figure 1 shows the number of doses administered to females by age group. Figure 2 shows the number of doses administered to females by ethnic group.

Figure 1: Vaccine doses administered to females by age group up to 21 October 2021. Source: COVID-19 Vaccination Events Qlik app, updated 21 October 2021 (accessed 21 October 2021).

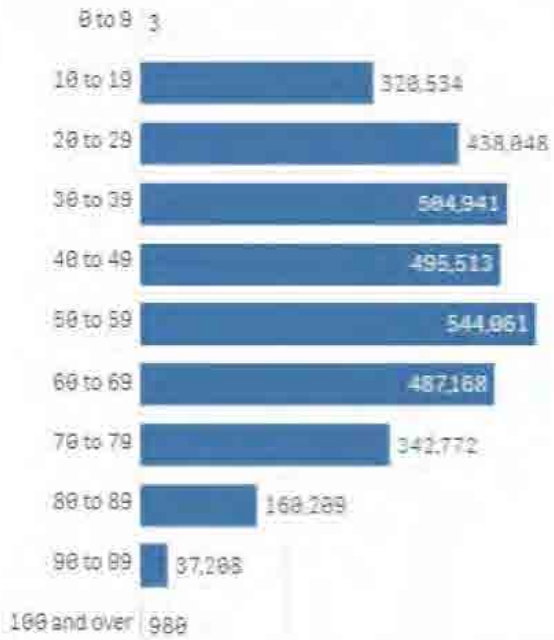
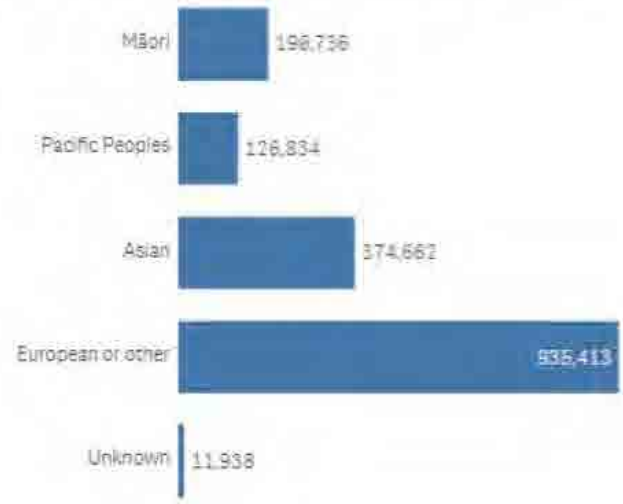


Figure 2: Vaccine doses administered to women of reproductive age (15-49 years) by ethnic group up to 21 October 2021. Source: COVID-19 Vaccination Events Qlik app, updated 21 October 2021 (accessed 21 October 2021).



SOURCE OF SAFETY CONCERN

There have been reports of AEFIs in pregnant women administered Comirnaty in New Zealand.

This report includes AEFI reports that have been coded with terms under the pregnancy, puerperium and perinatal conditions system organ class (SOC). The terms reported as of 21 October 2021 are spontaneous abortion, exposure during pregnancy, foetal hypokinesia and congenital abnormality.

There have been 13 cases of spontaneous abortion in New Zealand reported following administration of Comirnaty, as of 21 October 2021. s 9(2)(a) [redacted]

s 9(2)(a) [redacted]

The remaining three cases describe exposure during pregnancy/dizziness, palpitations/foetal hypokinesia, and congenital abnormalities.

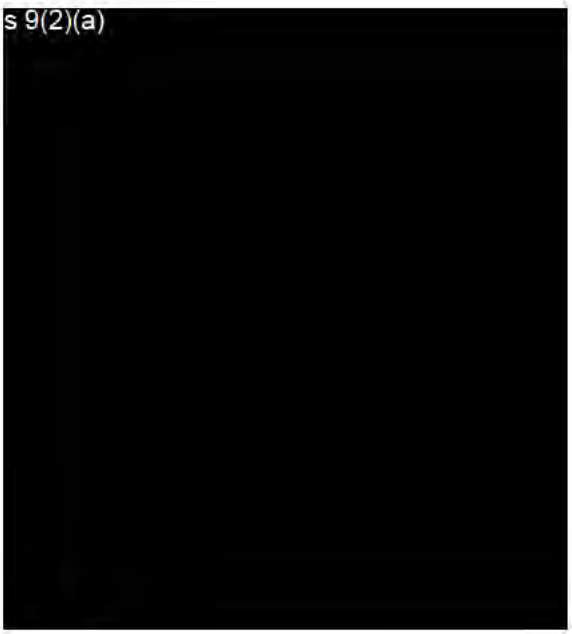
Annex 1 contains detailed information about the cases.

s 9(2)(a), s 9(2)(f)(iv) [redacted]

s 9(2)(a) [redacted]

s 9(2)(a)

s 9(2)(a)



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REVIEW OF THE AVAILABLE INFORMATION

New Zealand data sheet and international product information

Section 4.6 of the New Zealand data sheet includes the following information relating to use in pregnancy:

> 'There is limited experience with use of COMIRNATY in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition or post-natal development (see Fertility). Administration of COMIRNATY in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and fetus.'

The United Kingdom summary of product characteristics and Australian product information are identical to the New Zealand data sheet.

The Canadian product monograph states:

> 'The safety and efficacy of COMIRNATY in pregnant women have not yet been established. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/ fetal development, parturition, or post-natal development (see 16 NON-CLINICAL TOXICOLOGY).'

The United States prescribing information states:

> 'All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Available data on Pfizer-BioNTech COVID-19 Vaccine administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.
>
> In a reproductive and developmental toxicity study, 0.06 mL of a vaccine formulation containing the same quantity of nucleoside-modified messenger ribonucleic acid (mRNA) (30 mcg) and other ingredients included in a single human dose of Pfizer-BioNTech COVID-19 Vaccine was administered to female rats by the intramuscular route on four occasions: 21 and 14 days prior to mating, and on gestation days 9 and 20. No vaccine-related adverse effects on female fertility, fetal development, or postnatal development were reported in the study.'

s 9(2)(a), s 9(2)(f)(iv) [redacted]

s 9(2)(a), s 9(2)(f)(iv)

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s 9(2)(a), s 9(2)(f)(iv)

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s 9(2)(a), s 9(2)(f)(iv)

[redacted]

s 9(2)(f)(iv), s 9(2)(b)(ii)

[redacted]

Communications from international regulators, organisations and government departments

The New Zealand Ministry of Health, Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG), Canadian Ministry of Health, Royal College of Obstetricians and Gynaecologists (UK) and Centres for Disease Control and Prevention (US) have issued statements in support of routine COVID-19 vaccination of pregnant people. [5-9]

The WHO has published the following guidance on COVID-19 vaccination during pregnancy: [3]

> 'At present (April 2021), the WHO Strategic Advisory Group of Experts on Immunization (SAGE) recommends that pregnant women can receive COVID-19 vaccine if the benefits of vaccination outweigh the potential risks, such as occupational activities with unavoidable high risk of exposure, and pregnant women with co-morbidities which place them in a high-risk group for severe COVID-19 disease. In other words, vaccination for pregnant women should be considered on a case by case basis after consultation between the woman and her health care provider. To help pregnant women decide, they should be provided with information about the risks of COVID-19 in pregnancy, the likely benefits of vaccination in the local epidemiological context, and the current limitations of the safety data for the vaccines in pregnant women.

As more data become available these guidelines will be updated. Routine testing for pregnancy before COVID-19 vaccination is not recommended.'

The WHO has also issued guidance on communicating with pregnant and lactating women during COVID-19 vaccination sessions. [10]

Literature

Several studies describing the safety of COVID-19 vaccination during pregnancy are summarised below. A full list of studies identified relating to safety of COVID-19 vaccines in pregnancy is included in Annex 2.

Shimabukuro et al. 2021. Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons [11]

This study aimed to characterise the safety of mRNA vaccines (ie, Comirnaty and Spikevax) in pregnant people in the United States. Data from the 'v-safe after vaccination health checker' surveillance system, the v-safe pregnancy registry, and the Vaccine Adverse Event Reporting System (VAERS) obtained between December 2020 and February 2021 were evaluated.

The v-safe surveillance system is a voluntary smartphone-based active surveillance system, which sends links to online surveys immediately after vaccination through to one year after vaccination. V-safe is used to identify people who reported being pregnant, who are then invited to join the v-safe pregnancy registry. Detailed medical information is collected about the participants in the pregnancy registry via telephone interviews.

Adverse reaction reports in pregnant people from the spontaneous reporting system (VAERS) were also reviewed for the study. Reporting of pregnancy-related complications resulting in hospitalisation and congenital abnormalities is required of healthcare professionals under the conditions of the Emergency Use Authorisations for COVID-19 vaccines in the United States.

V-safe data was used to compare the reported proportions of local and systemic reactogenicity between pregnant and non-pregnant people. In the v-safe pregnancy registry, the outcomes of completed pregnancies were evaluated. The outcomes reported included pregnancy loss (spontaneous abortion and stillbirth) and neonatal outcomes (preterm birth, congenital anomalies, small size for gestational age, and neonatal death).

During the study period for the interim analysis, 35,691 v-safe participants identified as pregnant. The most frequently reported reactogenicity symptoms were injection-site pain, fatigue, headache, and myalgia, which were reported more frequently after the second dose. The reactogenicity profile was similar between pregnant and non-pregnant people. Nausea and vomiting was reported in a slightly higher proportion of pregnant people.

As of March 30 2021, there were 3,958 pregnant people who were vaccinated during the study period enrolled into the v-safe pregnancy registry, of whom 94% identified as healthcare personnel. There were 827 participants with a completed pregnancy of which 712 (86.1%) resulted in a live birth, 104 (12.6%) resulted in a spontaneous abortion, 1 (0.1%) resulted in still-birth and 10 (1.2%) resulted in other outcomes (induced abortion and ectopic pregnancy). Of the 104 spontaneous abortions, 96 (92.3%) occurred during the first trimester of pregnancy. The adverse outcomes in 724 live-born infants were pre-term birth (9.4%), small size for gestational age (3.2%) and major congenital abnormalities (2.2%). There were no neonatal deaths. None of the reports of major congenital abnormalities were associated with vaccination during the periconception period or first trimester. Proportions of adverse pregnancy and neonatal outcomes were similar to published incidences in the literature (table 2).

Table 2: Pregnancy loss and neonatal outcomes in published studies and v-safe pregnancy registry participants. Source: Shimabukuro TT, Kim SY, Myers TR, et al. 2021. Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons. New England Journal of Medicine 384(24): 2273-2282. DOI: 10.1056/NEJMoa2104983.

Participant-Reported Outcome	Published Incidence*	V-safe Pregnancy Registry†
	%	*no./total no. (%)*
Pregnancy loss among participants with a completed pregnancy		
Spontaneous abortion: <20 wk[15-17]‡	Not applicable	104
Stillbirth: ≥ 20 wk[18-20]	<1	1/725 (0.1)§
Neonatal outcome among live-born infants		
Preterm birth: <37 wk[21,22]	8–15	60/636 (9.4)¶
Small size for gestational age[23,24]‖	3.5	23/724 (3.2)
Congenital anomalies[25]**	3	16/724 (2.2)
Neonatal death[26]††	<1	0/724

* The populations from which these rates are derived are not matched to the current study population for age, race and ethnic group, or other demographic and clinical factors.

† Data on pregnancy loss are based on 827 participants in the v-safe pregnancy registry who received an mRNA Covid-19 vaccine (BNT162b2 [Pfizer–BioNTech] or mRNA-1273 [Moderna]) from December 14, 2020, to February 28, 2021, and who reported a completed pregnancy. A total of 700 participants (84.6%) received their first eligible dose in the third trimester. Data on neonatal outcomes are based on 724 live-born infants, including 12 sets of multiples.

‡ A total of 96 of 104 spontaneous abortions (92.3%) occurred before 13 weeks of gestation. No denominator was available to calculate a risk estimate for spontaneous abortions, because at the time of this report, follow-up through 20 weeks was not yet available for 905 of the 1224 participants vaccinated within 30 days before the first day of the last menstrual period or in the first trimester. Furthermore, any risk estimate would need to account for gestational week–specific risk of spontaneous abortion.

§ The denominator includes live-born infants and stillbirths.

¶ The denominator includes only participants vaccinated before 37 weeks of gestation.

‖ Small size for gestational age indicates a birthweight below the 10th percentile for gestational age and infant sex according to INTERGROWTH-21st growth standards (http://intergrowth21.ndog.ox.ac.uk). These standards draw from an international sample including both low-income and high-income countries but exclude children with coexisting conditions and malnutrition. They can be used as a standard for healthy children growing under optimal conditions.

** Values include only major congenital anomalies in accordance with the Metropolitan Atlanta Congenital Defects Program 6 Digit Code Defect List (www.cdc.gov/ncbddd/birthdefects/macdp.html); all pregnancies with major congenital anomalies were exposed to Covid-19 vaccines only in the third trimester of pregnancy (i.e., well after the period of organogenesis).

†† Neonatal death indicates death within the first 28 days after delivery.

There were 221 reports retrieved from VAERS describing vaccination of pregnant people. Of these, 155 (70.1%) described adverse events not specific to pregnancy, and 66 (29.9%) described adverse events relating to the pregnancy or neonate. There were 46 cases of spontaneous abortion, of which 37 were during the first trimester and two were during the second trimester. In seven cases, the trimester was unknown. There were three reports each of stillbirth, premature rupture of membranes, and vaginal bleeding, and no reports of congenital abnormalities.

The authors noted a number of limitations in the study, including:

- Comparison of proportions of adverse pregnancy and neonatal outcomes are limited by differences in the populations studied and are intended provide a crude sense only of any unexpected signals
- V-safe participants self-reported their pregnancy status, and data describing local and systemic reactogenicity may be subject to misclassification
- The survey data does not allow assessment of time to onset or duration of reactogenicity symptoms
- The data are preliminary, based on a small sample size, and mostly describe outcomes following third trimester vaccination
- The follow-up period was too short to capture first trimester vaccination and subsequent congenital abnormality outcomes
- The proportions of spontaneous abortion may not reflect true post-vaccination proportions because participants might have been vaccinated after the period of greatest risk in the first trimester, and early pregnancy losses may have been undetected
- At the time the study was conducted, most of the pregnancies involving vaccination during the first and second trimesters were ongoing
- The study uses data reported by participants, with limited information on other risk factors for adverse pregnancy and neonatal outcomes
- VAERS is subject to the limitations of passive surveillance

- The total number of vaccine doses administered to pregnant women is unknown and creates limitations to estimating rates of adverse pregnancy and neonatal outcomes.

This preliminary data does not indicate any safety signals in pregnant people administered mRNA vaccines. Continued monitoring is needed to add to these results.

Zauche et al. 2021. Receipt of mRNA Covid-19 Vaccines and Risk of Spontaneous Abortion [12]

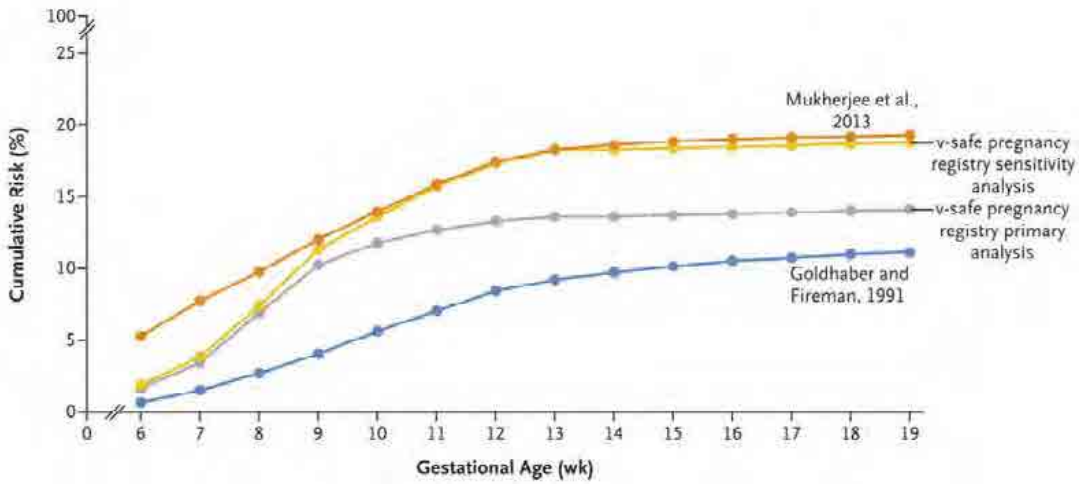
This research letter uses data from the Centres for Disease Prevention (CDC) v-safe pregnancy registry to determine the cumulative risk of spontaneous abortion from 6 to less than 20 weeks of gestation.

A total of 2456 participants were included in the study, of which 2022 reported ongoing pregnancies at 20 weeks and 165 reported a spontaneous abortion after six weeks of gestation and before 20 weeks of gestation. The remainder were not followed up at 20 weeks gestation or later, or reported another pregnancy outcome before 20 weeks gestation.

The cumulative risk of spontaneous abortion was calculated according to gestational week using life table methods. Another analysis was age-standardized with the use of data on the risk of spontaneous abortion according to maternal age group. A sensitivity analysis was conducted that assumed that 65 participants with ongoing pregnancy during the first trimester that could not be reached for second trimester follow-up had a spontaneous abortion.

This data was compared to historical cohorts that represent the upper and lower ranges of spontaneous abortion risk. The cumulative risks calculated in this study fall within this range (figure 6).

Figure 6: Cumulative risk of spontaneous abortion in the v-safe COVID-19 vaccine pregnancy registry and in two historical cohorts. Data from Mukherjee et al were presented as race-specific rates and are provided here for white women to maximize comparability with the v-safe pregnancy registry. Source: Zauche et al. 2021. Receipt of mRNA Covid-19 Vaccines and Risk of Spontaneous Abortion. New England Journal of Medicine 385(16): 1533-1535. DOI: 10.1056/NEJMc2113891.



Blakeway et al. 2021. COVID-19 Vaccination During Pregnancy: Coverage and Safety [13]

This cohort study aimed to investigate the uptake and safety of COVID-19 vaccination among pregnant women in the United Kingdom. The cohort was derived from those who gave birth at St George's University Hospitals National Health Service Foundation Trust, London, United Kingdom, between March 1, 2020, and July 4, 2021. The primary outcome in this study was vaccine uptake, and secondary outcomes were perinatal safety outcomes, including stillbirth, preterm birth, foetal and congenital abnormalities, and intrapartum complications. People who received a COVID-19 vaccine (Comirnaty, Spikevax or AstraZeneca) were compared to a propensity score-matched cohort of people with balanced propensity scores.

Data were available for 1328 pregnant women, of whom 140 received at least one dose of a COVID-19 vaccine. Of the vaccinated group, 127 (90%) received an mRNA vaccine. The vaccination was administered during the third trimester in 85.7% of people and during the second trimester in 14.3% of people.

The rates of adverse pregnancy outcomes were similar between vaccinated and unvaccinated people (table 3). A statistically significant increase in intrapartum pyrexia lost this significance when people with antenatal COVID-19 infection were excluded.

Table 3: Pregnancy outcomes among propensity score-matched women who received at least 1 dose of the COVID-19 vaccine. Source: Blakeway et al. COVID-19 Vaccination During Pregnancy: Coverage and Safety. American Journal of Obstetrics & Gynecology. DOI:10.1016/j.ajog.2021.08.007 (accessed 2 September 2021).

Variables	At least 1 dose during pregnancy (n=133)	Did not receive a vaccine during pregnancy (n=399)	Effect magnitude (95% CI)[a]	*P* value[a]
Intrapartum complications				
Pyrexia	5 (3.7)	4 (1.0)	3.85 (1.01–14.6)	.046
Suspected chorioamnionitis	0 (0.0)	2 (0.5)	NE	NE
Placental abruption	0 (0.0)	0 (0.0)	NE	NE
Postpartum hemorrhage	13 (9.8)	36 (9.0)	1.09 (0.56–2.12)	.795
Birthweight *z* score	−0.09 (−0.65 to 0.65)	−0.13 (−0.83 to 0.51)	0.04 (-0.16–0.24)	.427
Small for gestational age at birth	16 (12.0)	48 (12.0)	1.00 (0.55–1.82)	>.999
Fetal abnormalities	3 (2.2)	10 (2.5)	0.89 (0.24–3.31)	.871
Mode of delivery				
Unassisted vaginal delivery	71 (53.4)	221 (55.4)	0.92 (0.62–1.36)	.687
Instrumental delivery	21 (15.8)	42 (10.5)	1.59 (0.90–2.80)	.106
Cesarean delivery	41 (30.8)	136 (34.1)	0.86 (0.56–1.31)	.490
Stillbirth	0 (0.0)	1 (0.2)	NE	NE
High-dependency unit admission	8 (6.0)	16 (4.0)	1.53 (0.64–3.66)	.337
Neonatal intensive care unit admission	7 (5.3)	20 (5.0)	1.05 (0.43–2.54)	.909

Data are presented as number (percentage) or mean (interquartile range), unless otherwise indicated. Cases and controls were matched 1:3 using propensity scores calculated from the index of multiple deprivation quintile, self-reported ethnicity, antenatal medication, pregestational diabetes mellitus, maternal age, and antihypertensive medication.

CI, confidence interval; *MD*, mean difference; *NE*, not estimable; *OR*, odds ratio.

[a] Calculated using generalized estimation equations using matched group identifications as clusters.

Blakeway et al. COVID-19 vaccination during pregnancy. Am J Obstet Gynecol 2021.

The authors noted the following limitations of the study:

- Median time to birth after vaccination was one month
- None of the participants were vaccinated in the first trimester of pregnancy and only 15% were vaccinated in the second trimester
- People without vaccination records were not included in the study, which may have led to selection bias
- The study was not sufficiently powered to detect small effect sizes and 95% confidence intervals were wide.

This study contributes to the evidence of safety of mRNA vaccination during pregnancy, particularly during the third trimester.

Bleicher et al. 2021. Early exploration of COVID-19 vaccination safety and effectiveness during pregnancy: interim descriptive data from a prospective observational study [14]

This interim observational study analysis examines short-term pregnancy outcomes reported after vaccination of pregnant women in Israel. Vaccinated and non-vaccinated women were recruited through social media and information was collected using a questionnaire. The primary outcomes

were composite pregnancy complications such as vaginal bleeding, pregnancy loss during first trimester, pregnancy loss during second trimester, gestational diabetes, premature birth, premature contractions, and foetal growth restriction. Secondary outcomes were vaccine side effects, COVID-19 infection, uptake of vaccination and reasons for refusal of vaccination.

The characteristics of the vaccinated and non-vaccinated women completing the initial questionnaire were somewhat similar, but there was a higher rate of previous pregnancy loss in the unvaccinated group. It is unclear if there was differential loss to follow-up.

The initial and follow-up questionnaires were answered by 326 women, of whom 202 were vaccinated. Of the vaccinated group, 17.8% were vaccinated in the first trimester, 54.5% were vaccinated in the second trimester, and 27.7% were vaccinated in the third trimester.

The rate of composite pregnancy complications was similar between vaccinated and non-vaccinated group (15.8% vs 20.1%). First trimester pregnancy loss was reported by two people in the vaccinated group and one in the non-vaccinated group.

This analysis is limited due to self-reporting of outcomes and short-term follow-up. The numbers of reported adverse pregnancy outcomes were too small to make meaningful comparisons. The study is ongoing.

Trostle et al. 2021. COVID-19 vaccination in pregnancy: early experience from a single institution [15]

This study describes pregnancy outcomes for 424 people at a single medical centre who were vaccinated against COVID-19 during pregnancy. Of these 424 people, 29.2% were first vaccinated during the first trimester, 45.5% during the second trimester and 25.2% during the third trimester. Comirnaty was administered to 78.3% of participants and Spikevax was administered to 21.7% of participants.

Nine people had spontaneous abortions, of which eight were during the first trimester and one was during the second trimester. The rate of spontaneous abortion among women vaccinated during the first trimester was 6.5%. Of the women included, 85 delivered liveborn infants. There were no stillbirths. The rate of pre-term birth was 5.9%. Of the liveborn infant, 12.2% were small for gestational age. No concerning trends were identified. The study was limited by a small sample size and lack of a matched control group.

Public Interest

There is significant public concern about the safety of COVID-19 vaccination during pregnancy, likely due in part to unsubstantiated claims of fertility concerns associated with COVID-19 vaccination.

Expert Advice

It is recommended that the COVID-19 Vaccine Independent Safety Monitoring Board (CV-ISMB) is updated on the spontaneous reporting data in pregnant women that is available so far.

Conclusions and Proposed Actions

In general, there are no safety concerns associated with the use of non-live vaccines in pregnancy. Caution around live attenuated vaccines is based on the theoretical risk of placental transfer of attenuated virus and subsequent infection of the foetus. However, evidence of foetal harm after vaccination has not been identified [1, 2].

Pregnant women with symptomatic COVID-19 appear to have an increased risk of intensive care unit admission, mechanical ventilation and death in comparison with non-pregnant women of reproductive age, and may also be at increased risk of preterm birth [3].

There have been 13 reports of spontaneous abortion in New Zealand following administration of Comirnaty to pregnant people, s 9(2)(a) [redacted] Spontaneous abortion is common, occurring in around 10% of clinically recognised pregnancies. This risk increases with age [4]. The reports received to date do not highlight any concerning trends, although they contain limited information.

The published literature to date has not highlighted safety concerns around COVID-19 vaccination of pregnant women, although results are preliminary.

Reports of pregnancy related AEFIs in New Zealand should continue to be closely monitored.

RECOMMENDATIONS

It is recommended that:

1.	The CV-ISMB is updated on the spontaneous reporting data in pregnant women	Yes
2.	This topic should continue to be monitored through routine pharmacovigilance activities	Yes

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Updated case reports myocarditis/pericarditis/myopericarditis

- Up to 13 October: 156 cases reported in NZ.
- After review with CARM: 38 removed from analysis because diagnosis unlikely or no diagnosis made.
- Remaining cases: 118

Of these:

- 61 were reported after dose 1
- 57 were reported after dose 2

Document 6

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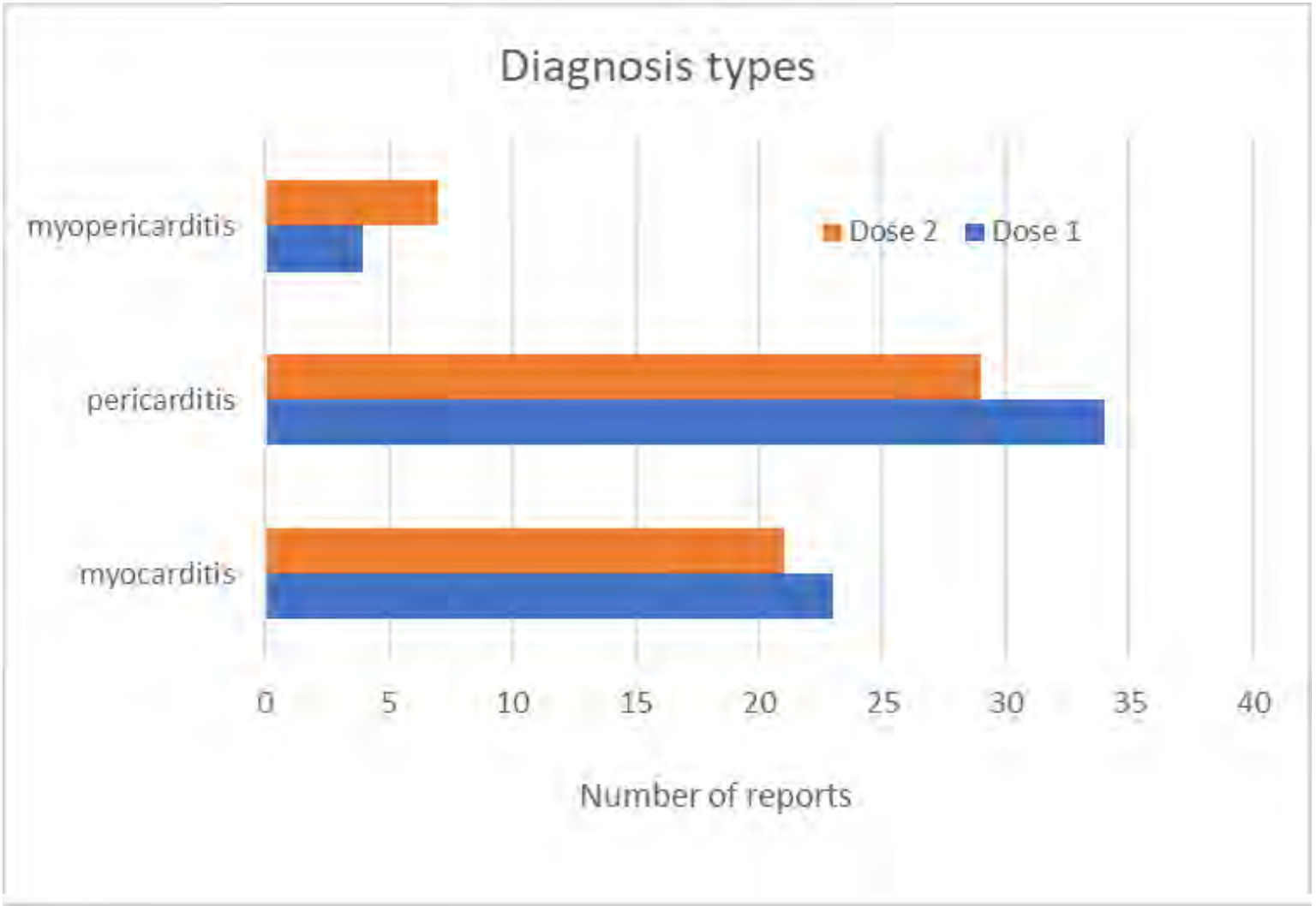
Document 6

Diagnosis type following dose 1 or dose 2



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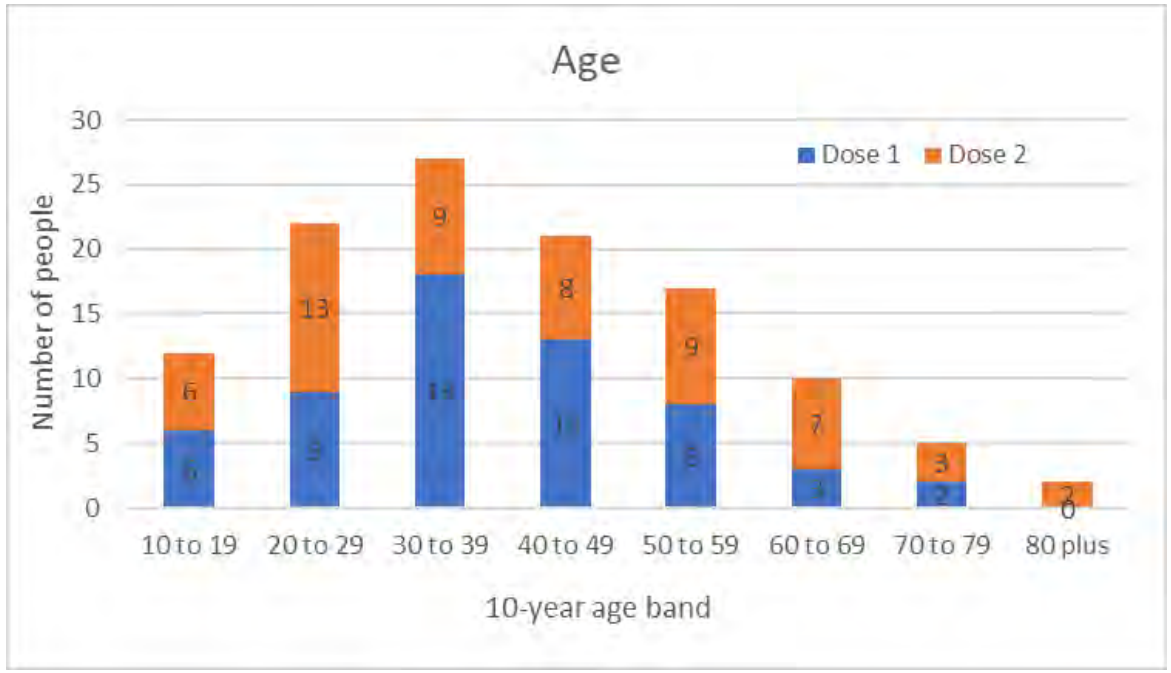
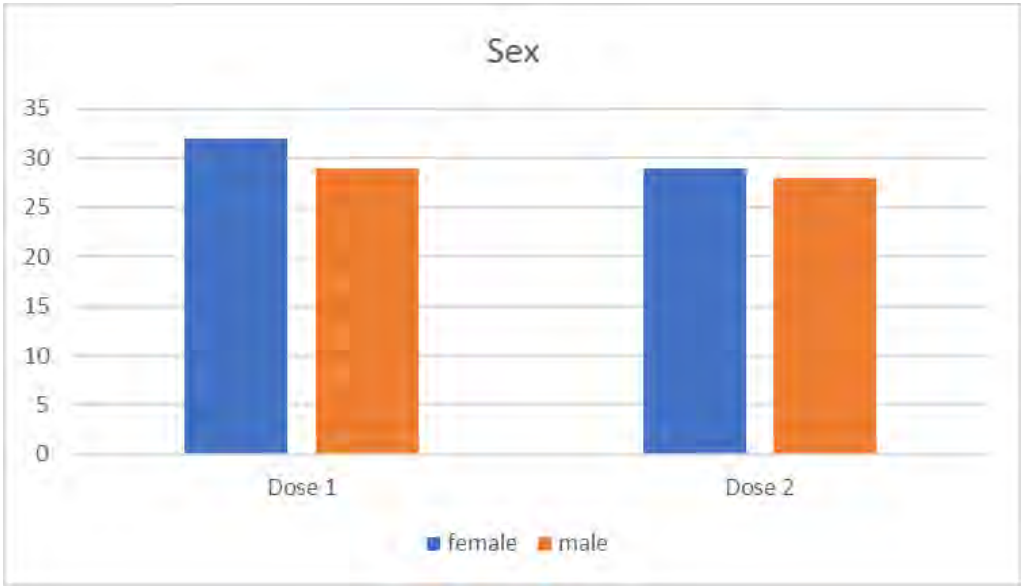
Document 6

Age bands and gender – all 3 diagnoses





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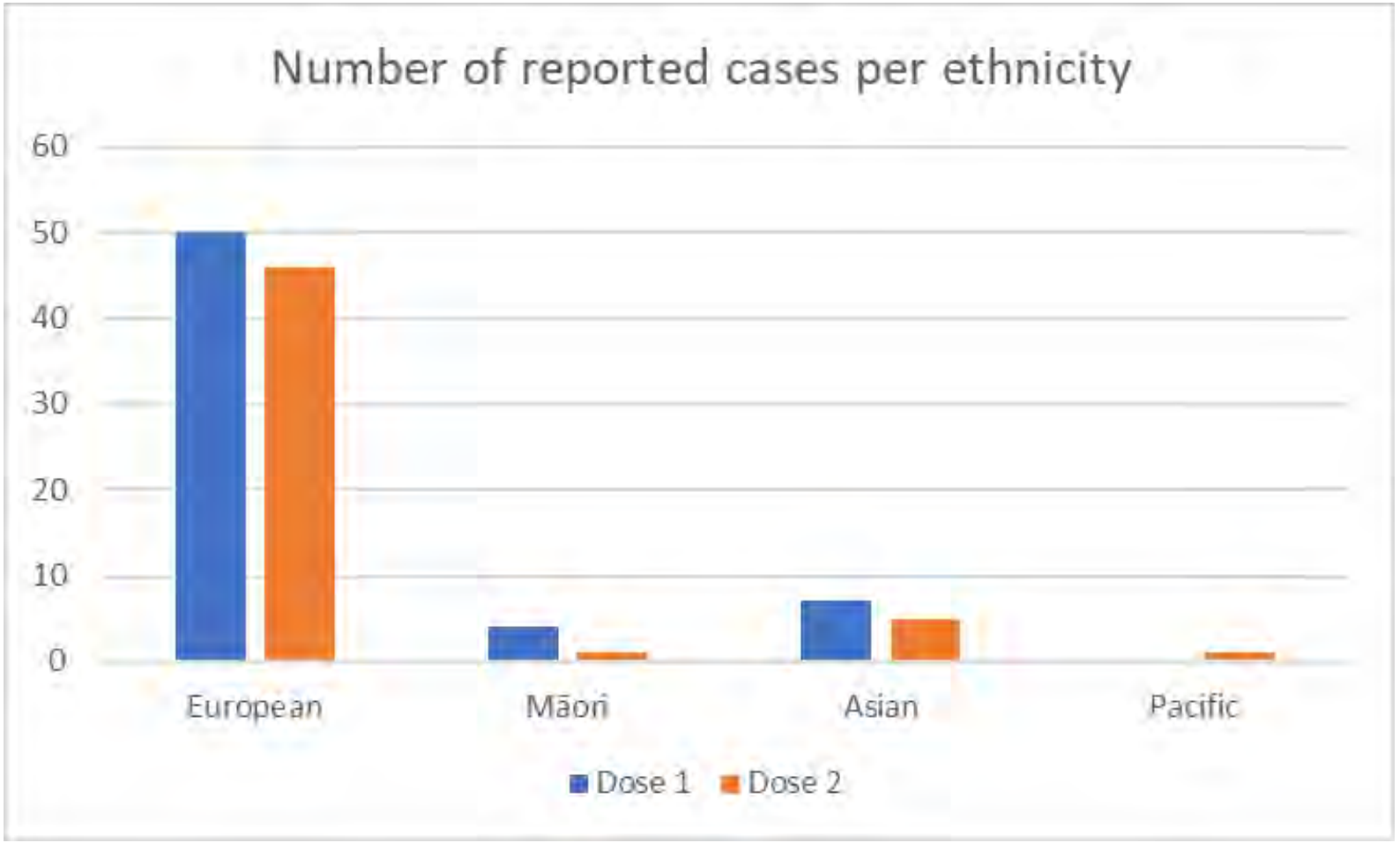
Ethnicity – all 3 diagnoses



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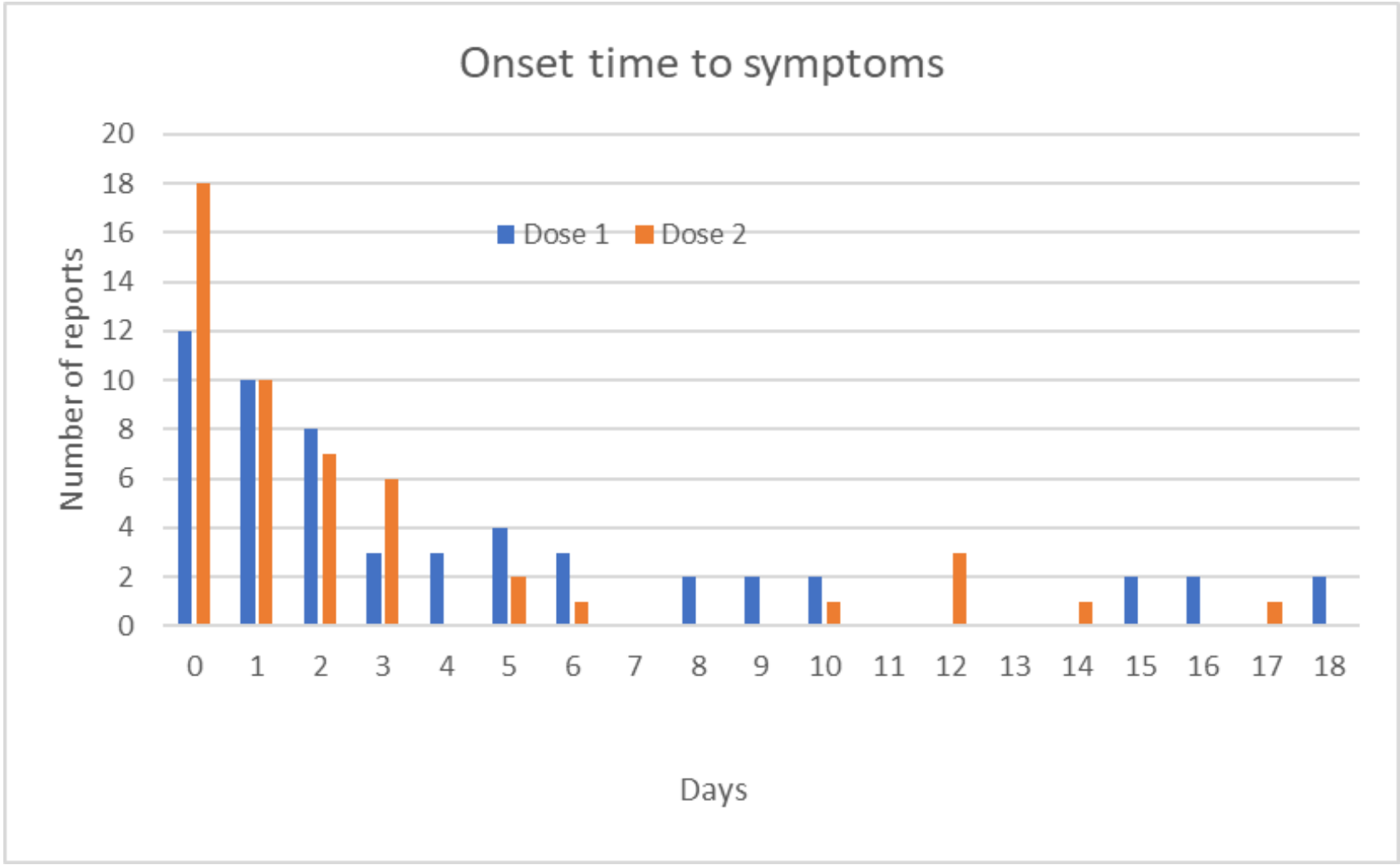
Onset time to symptoms (days) – all 3 diagnoses



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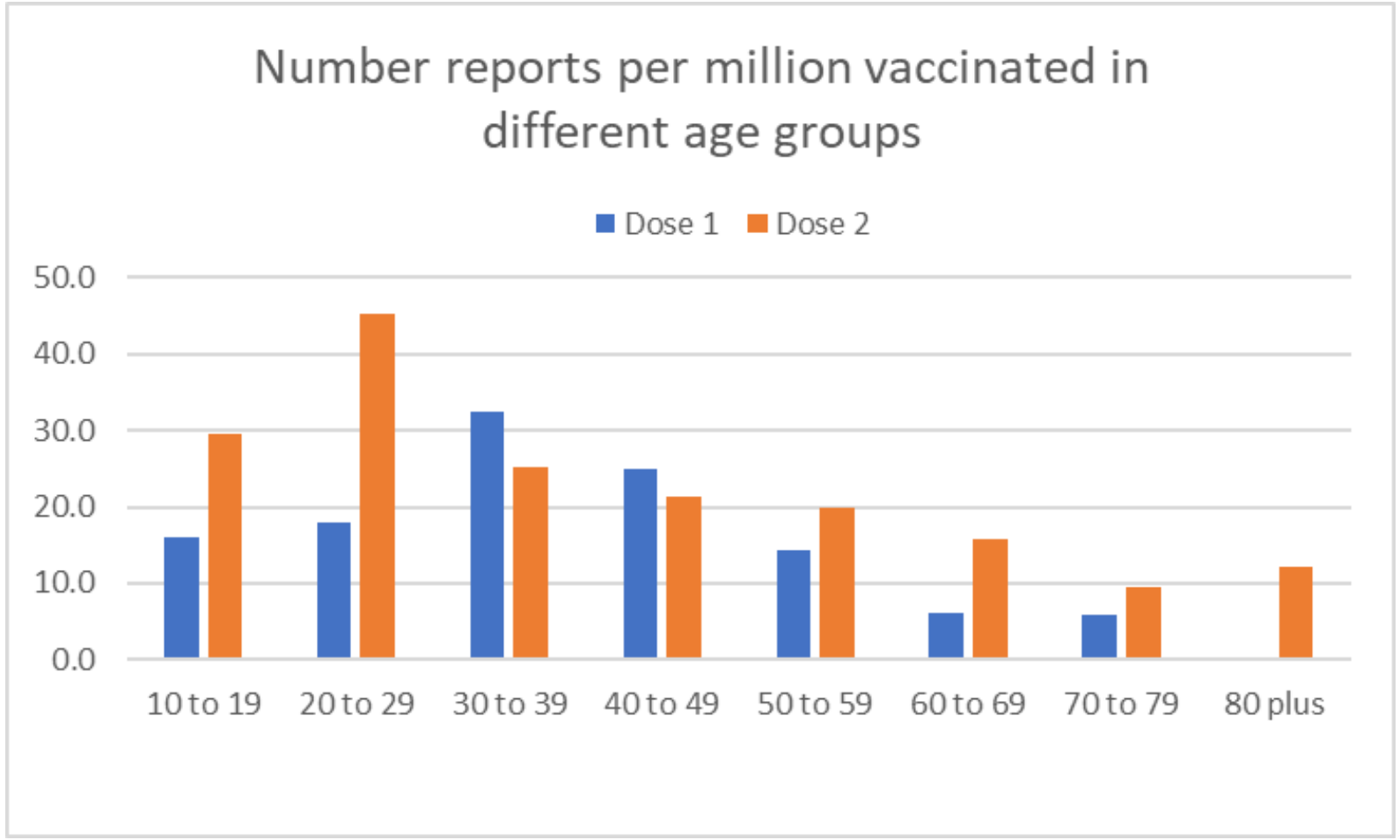
Reports per million vaccinated – all 3 diagnoses



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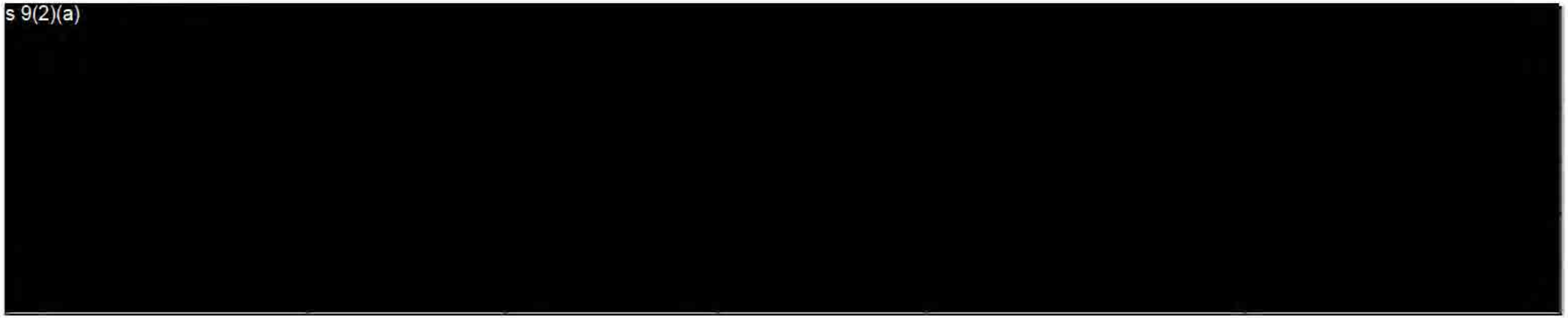
Rate of myo-, peri-, myopericarditis per million vaccinated



Document 7

Myo(peri)carditis overview

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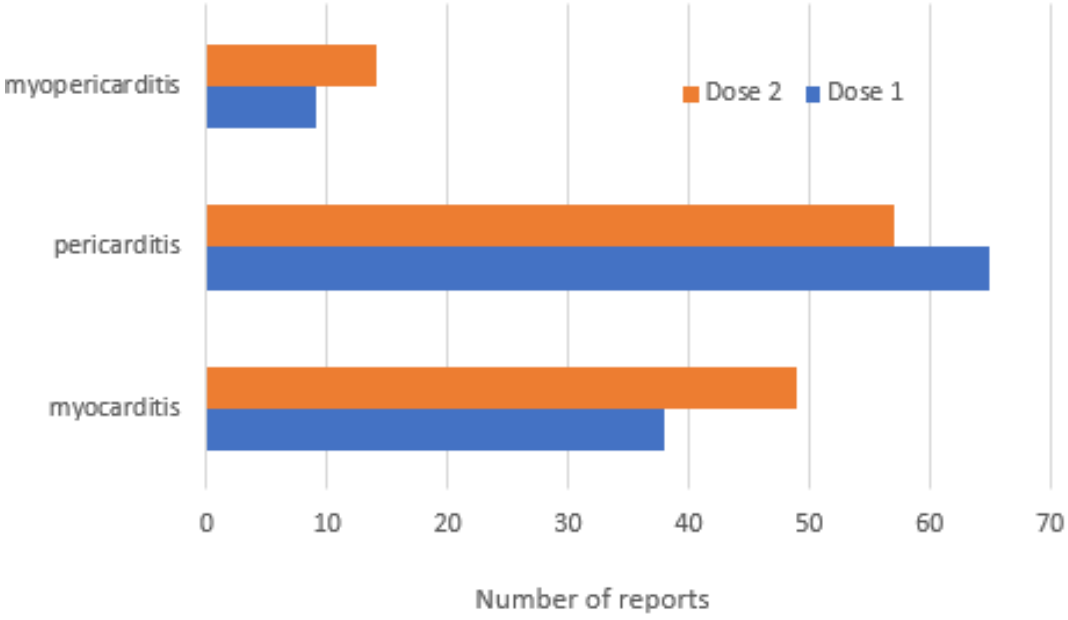
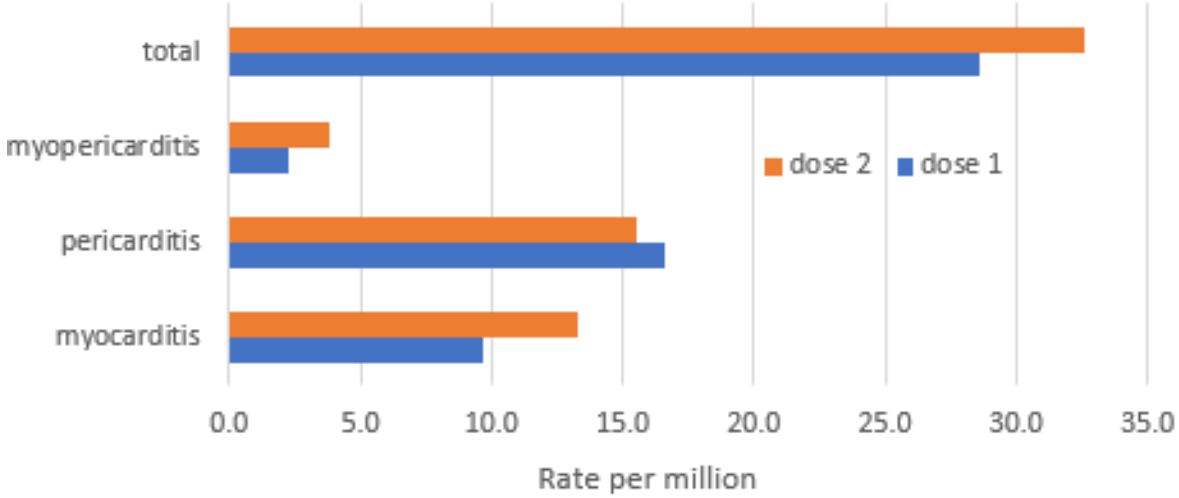
2021

Document 7

Diagnosis types

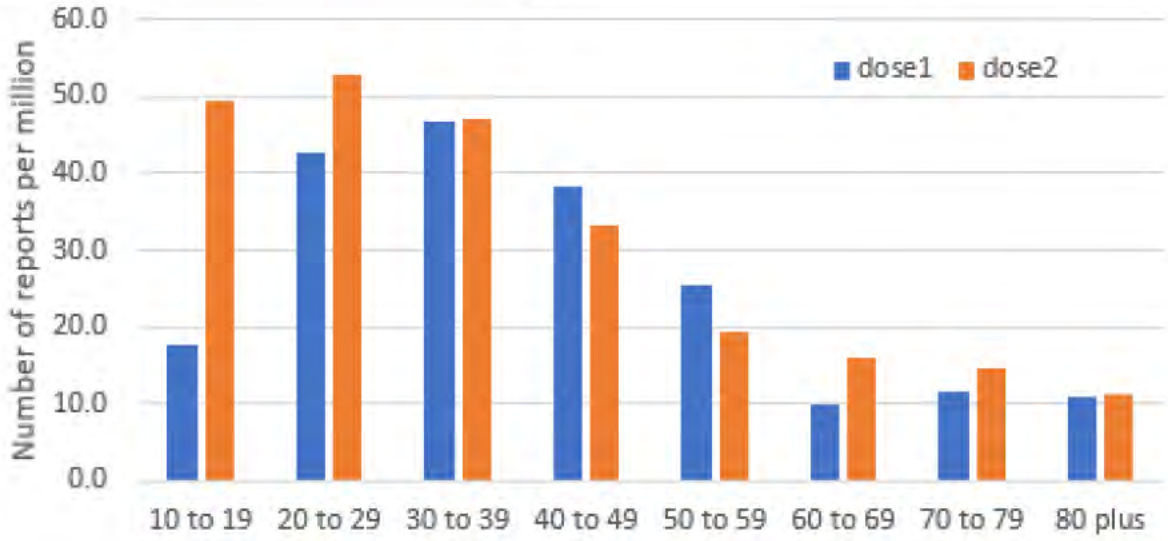




Document 7

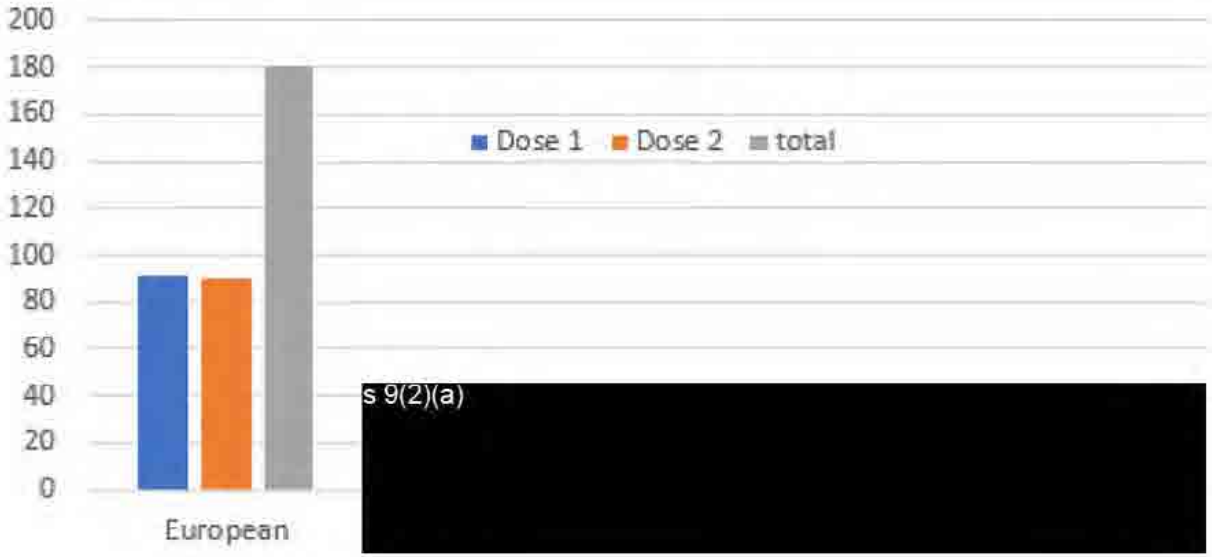
Age

s 9(2)(a)



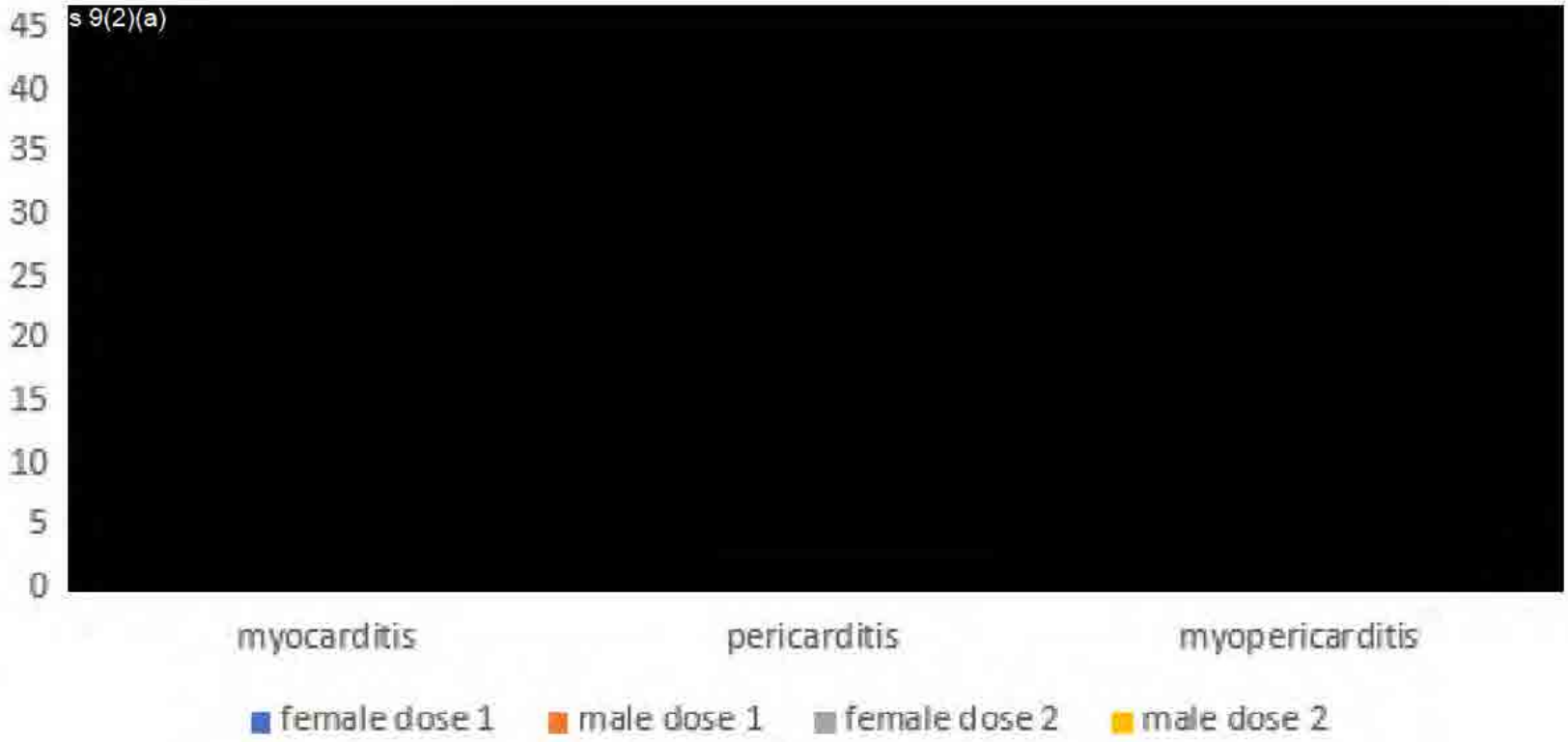
Document 7

Gender and ethnicity



Document 7

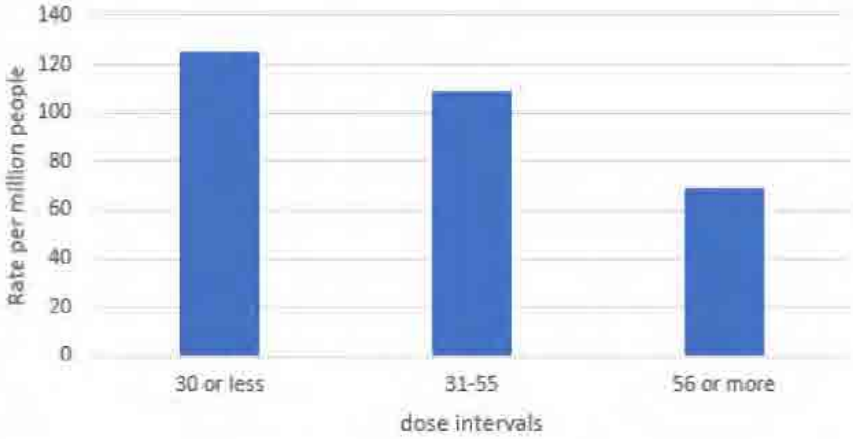
Diagnosis, dose and gender

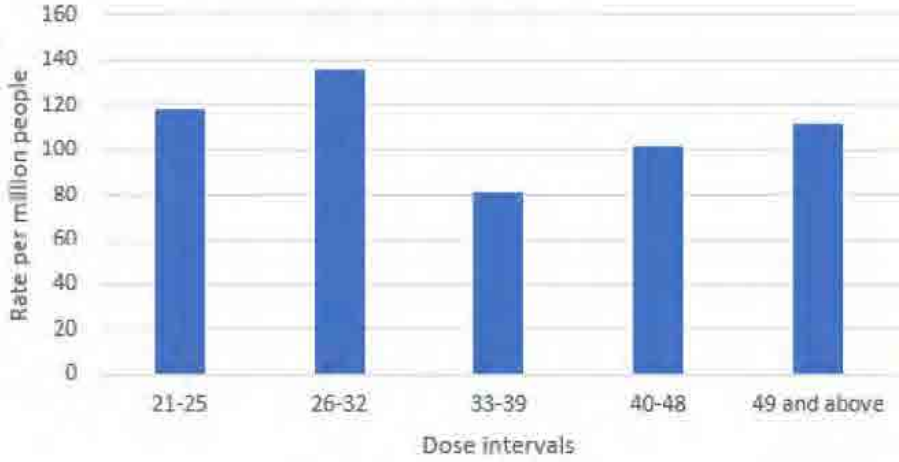


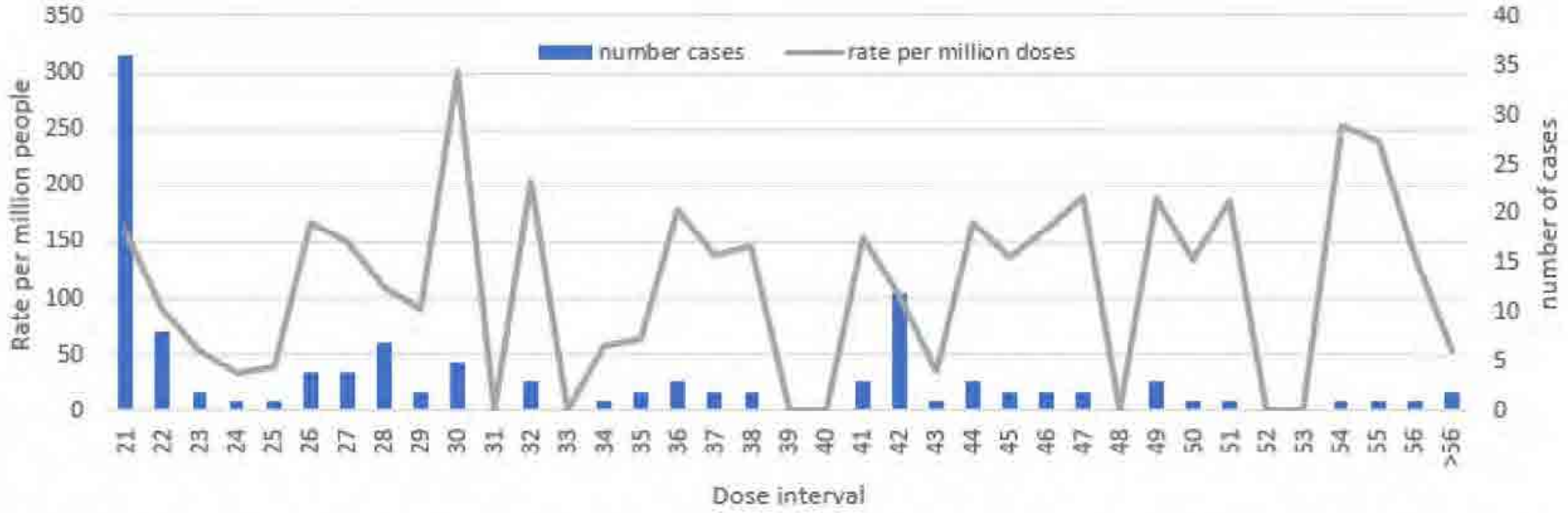
s 9(2)(g)(ii)

Document 7

Dose interval – all cases





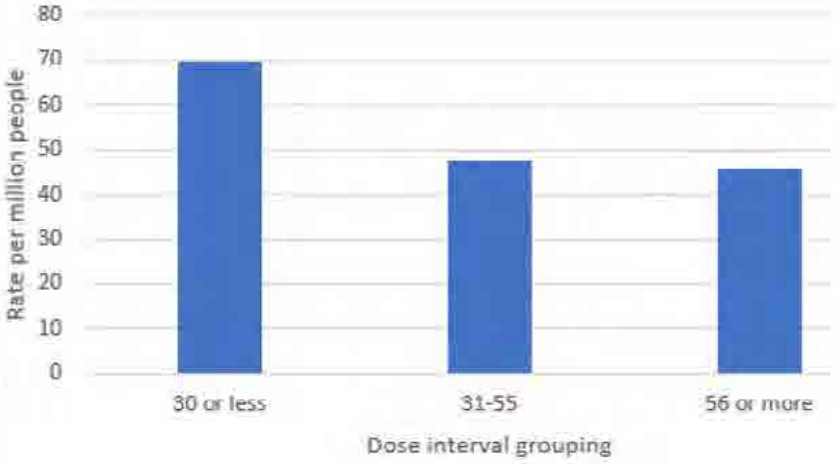


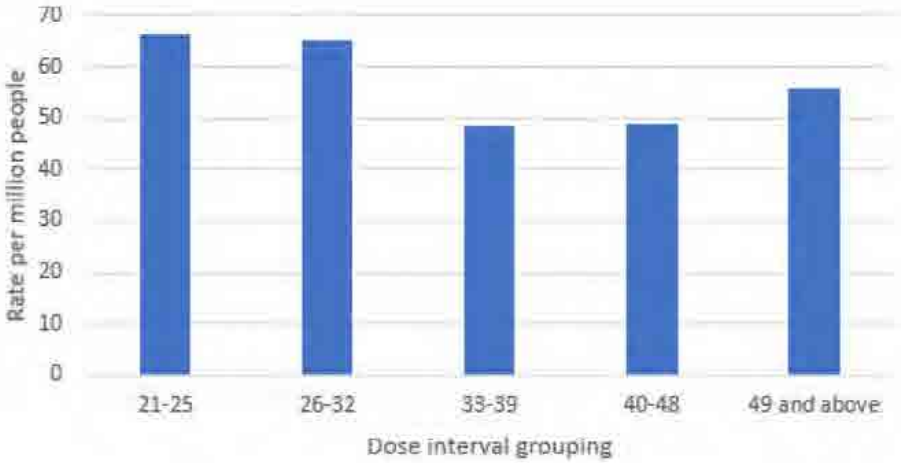
17 people reporting after dose 1 went on to have dose 2, no further report received.

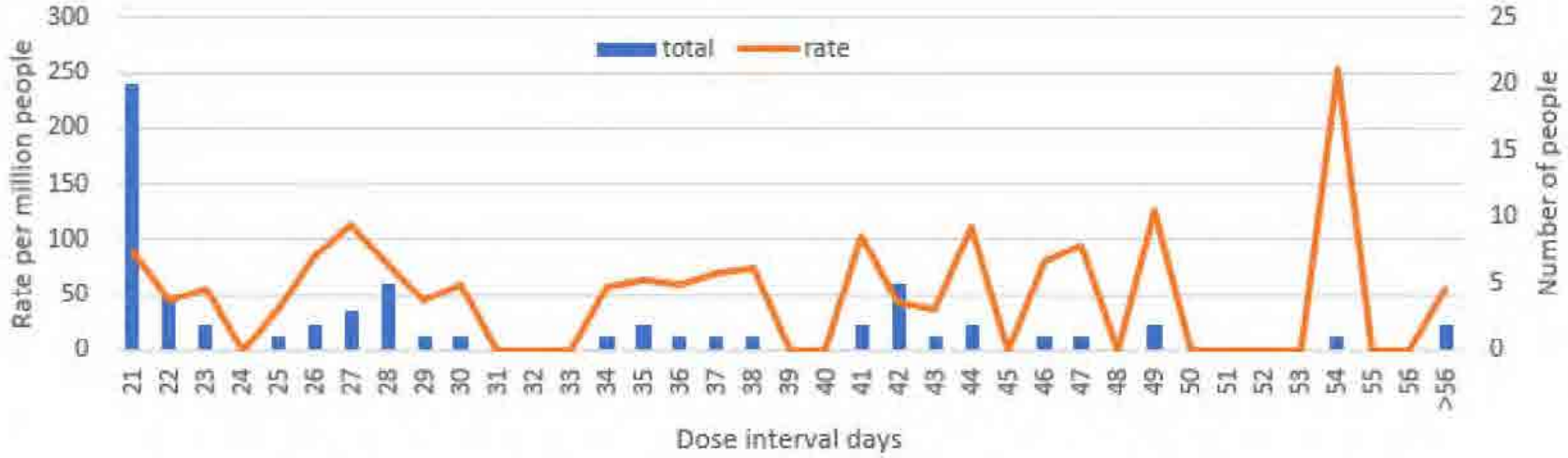
10 reports of pericarditis 7 reports of myocarditis

s 9(2)(g)(ii)

Dose interval- myocarditis

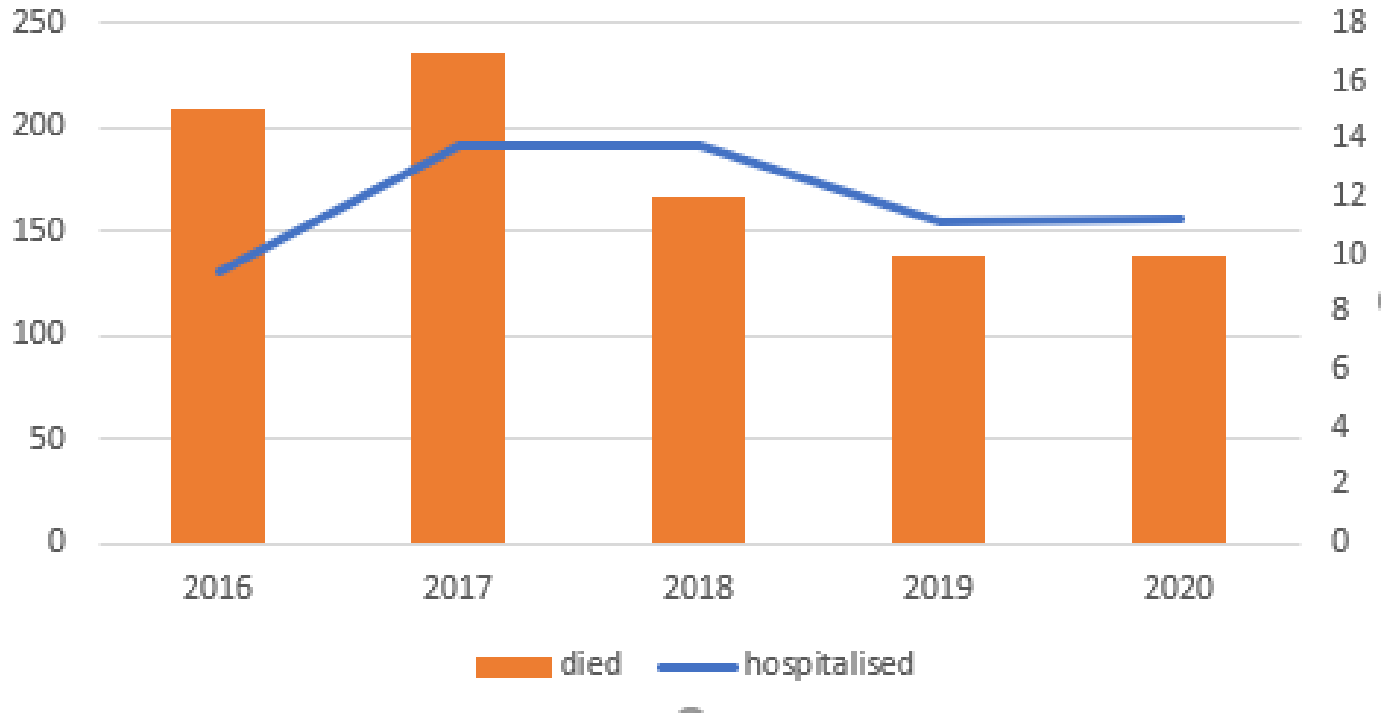






Myocarditis fatality rate

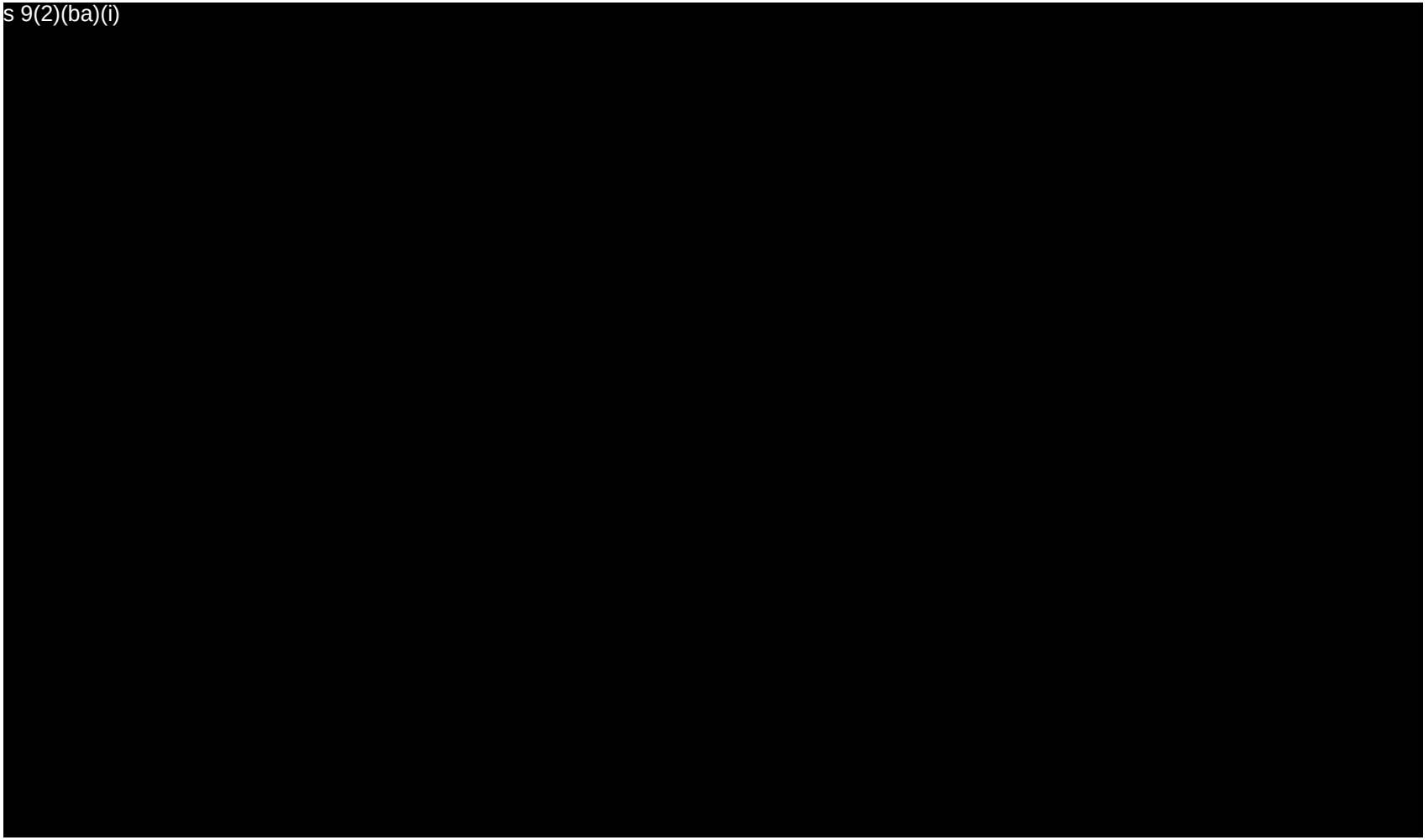
Number of people hospitalised with a principal diagnosis of myocarditis and number of deaths from myocarditis per year



Mean death rate in this time period 7.8%

Document 7

International information

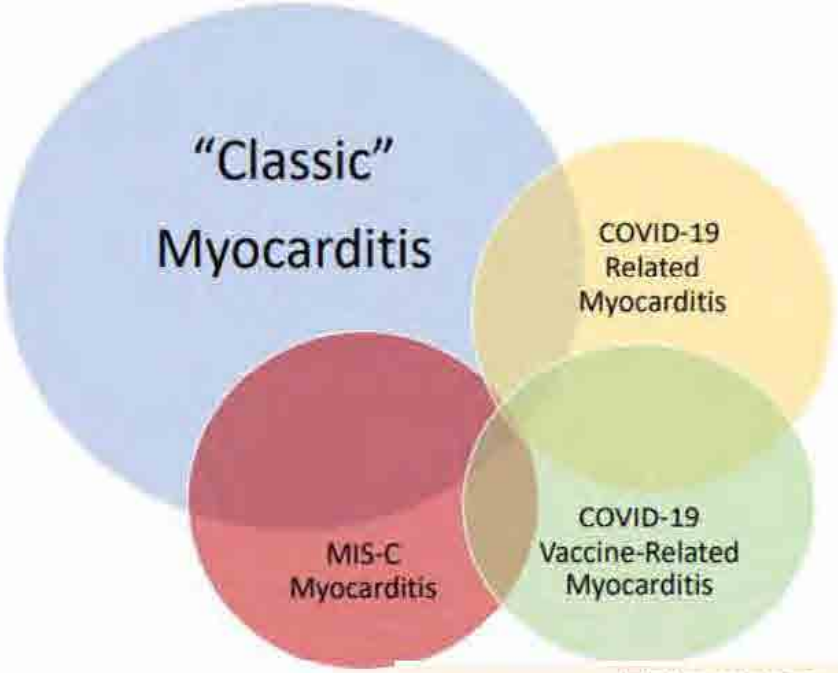


Literature cases

- **Abbate et al (US)-** Approximately 21 h after admission, patient with fulminant myocarditis temporally associated with Comirnaty died due to recurrent cardiac arrest and refractory shock.
- **Choi et al (South Korea)** - A 22-year-old man who developed chest pain 5 days after the first dose of the BNT162b2 mRNA vaccine died 7 hours later.
- **Chouchana et al (Vigibase)** - June 2021 22 fatal myo/pericarditis reports for mRNA vaccines.
- **Ho et al (Singapore)** – One patient with vaccine induced myocarditis died after a total of 9 million doses of mRNA vaccines.
- **Lane et al (spontaneous data from UK, EU and US)** - Post-mortem examination revealed myocarditis as the cause of death in one 65-year-old male. This patient had pre-existing cardiac disease, therefore it was not conclusively determined whether exposure to the vaccine resulted in this patient's death.
- **Mevorach et al (Israel)** – from 136 cases one person with fulminant myocarditis died.
- **Pillay et al (systematic review)** - Almost all reports of death are from unverified cases and of unclear cause**.**
- **Schneider et al (Germany) -** In one case (65M) after vaccination with Comirnaty, myocarditis was found to be the cause of death. (likely Lane et al case)

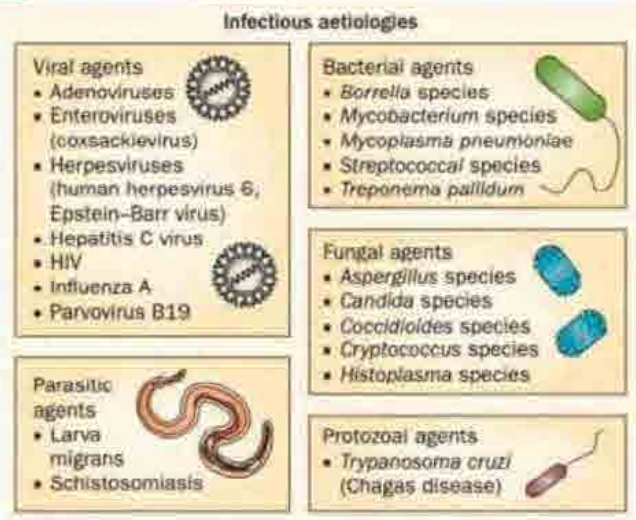
Document 7

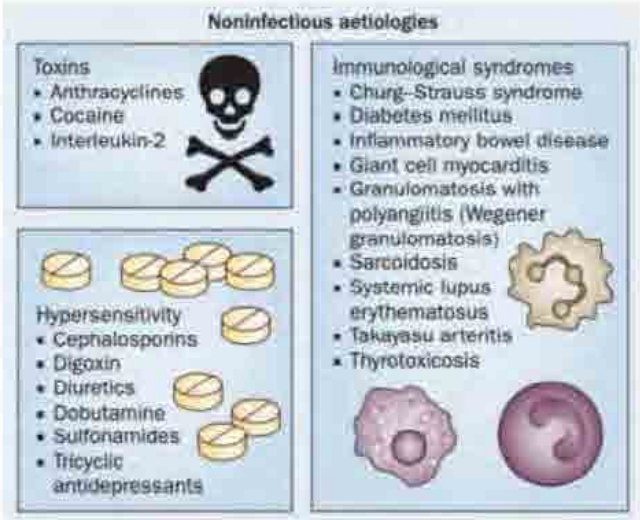
CDC review of myocarditis-1



US pre-covid epidemiology

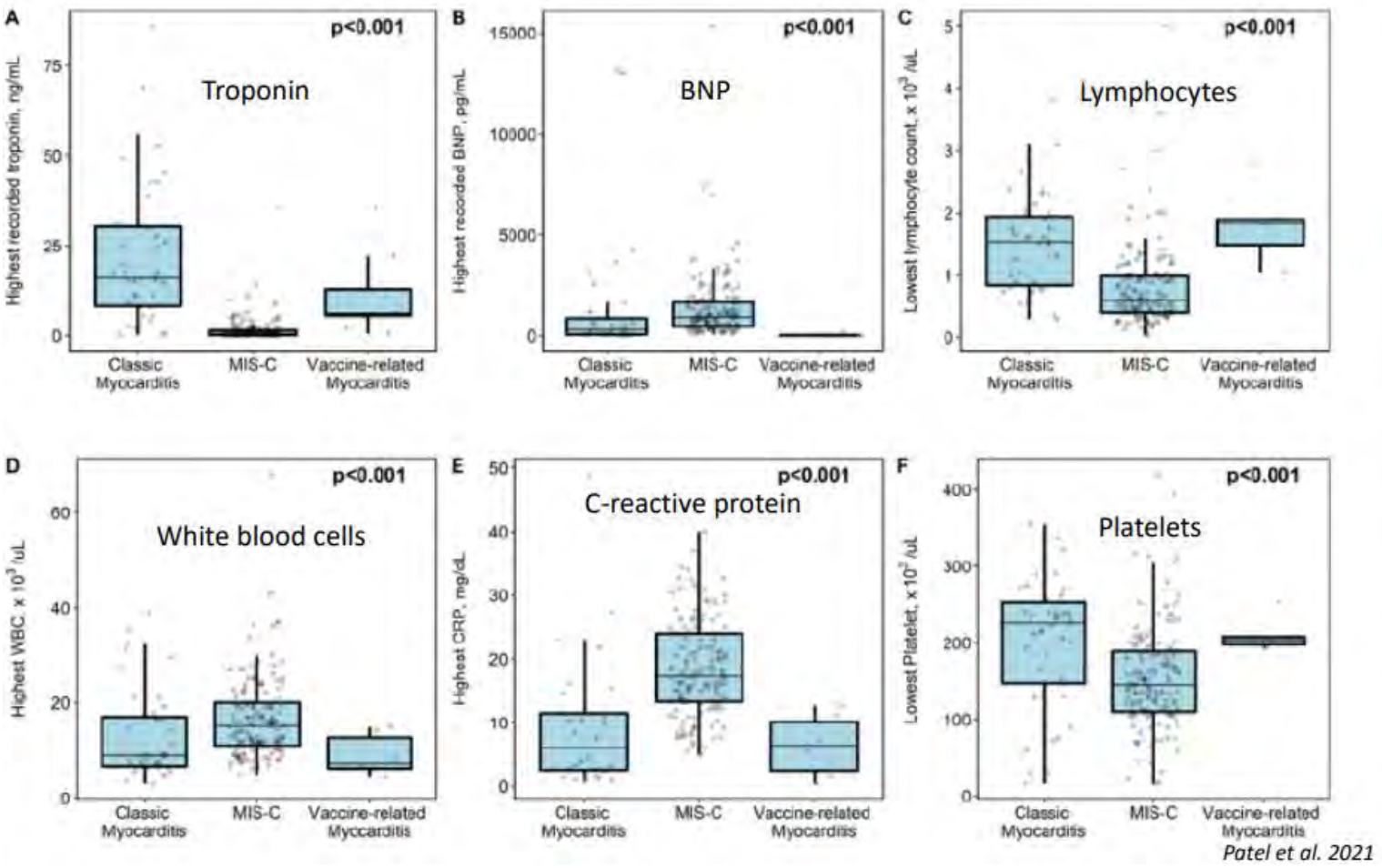
- Children
  - Annual incidence 0.8 per 100,000
    - In persons aged 15-18 years, 1.8 per 100,000 in 2015-2016
  - 66% male
  - Mortality 4-7%, transplant 4-9%





Document 7

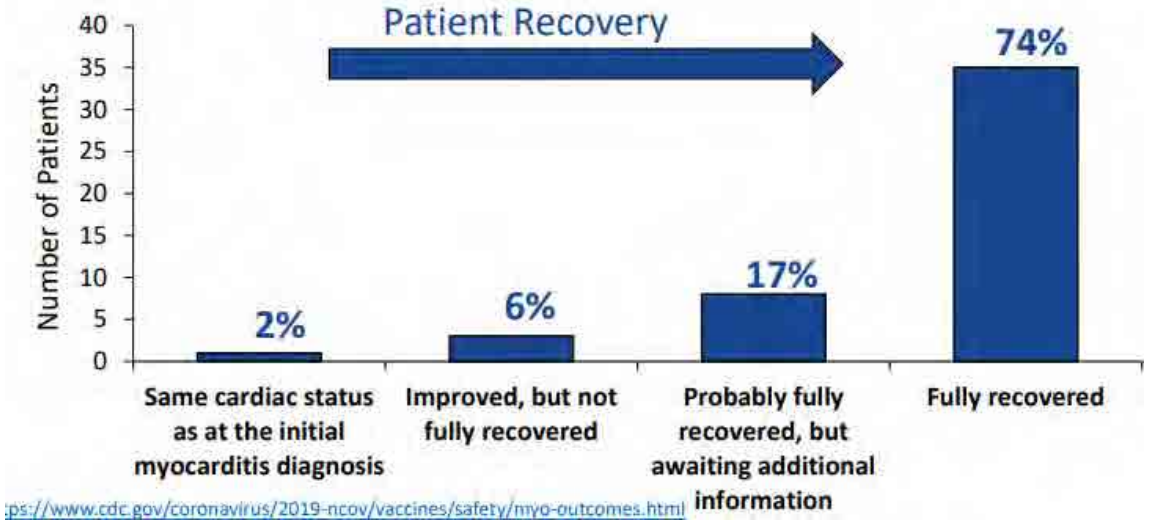
CDC-2



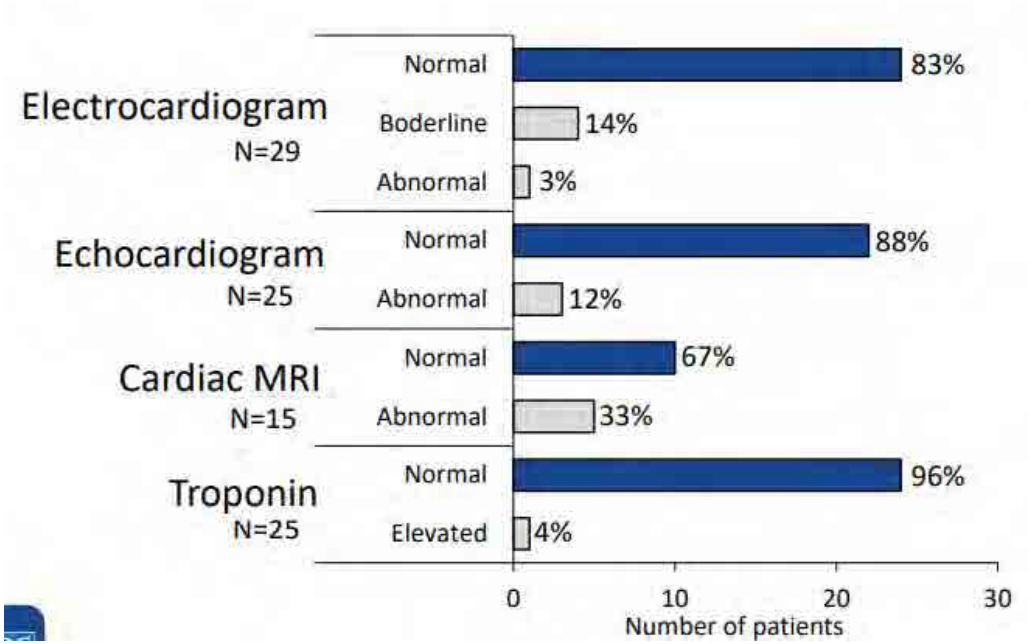
Patel et al. 2021

Document 7

CDC- follow up



ps://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/myo-outcomes.html



CV-ISMB 8 December 2021 Meeting Minutes

Date:	08 December 2021
Time:	4:00-6:00 pm
Location:	Ministry of Health & Microsoft Teams
Chair:	Mr John Tait
Attendees:	Dr Enver Yousuf, Dr Hilary Longhurst, Saskia Schuitemaker, Dr Nick Cutfield, Professor Thomas Lumley, Dr Owen Sinclair, Professor Ralph Stewart, Dr Kyle Eggleton, Dr Tom Hills, Professor Chris Frampton, Associate Professor Matt Doogue, Professor Lisa Stamp, Dr Anja Werno, Dr Laura Young, Associate Professor Michael Tatley, Dr Ian Town
Ministry of Health Attendees:	s 9(2)(g)(ii) [redacted]
Guests:	s 9(2)(a) [redacted]
Apologies:	Dr Maryann Heather

	Agenda Item
1	Karakia & Welcome
2	Overview of meeting - The Chair described the purpose of this meeting was to discuss three recent fatal cases where myocarditis following vaccination with Comirnaty which had been reported. - It was asked that members offer conclusions on their clinical opinion around whether the Comirnaty vaccine had a causal relationship to the myocarditis. - The Chair further reminded members that the outcome of the meeting must also include the generation of any recommendations for the Programme and for the Board to create a communication that is to be published for the public at the earliest time possible.
3	Case 1 s 9(2)(a) [redacted] presentation and discussion *CARM described the circumstances of the case:* - s 18(c)(ii) [redacted]

s 18(c)(ii) [redacted]

Discussion

- s 9(2)(g)(i), s 18(c)(ii) [redacted]
- It was asked by the pathologist if she could take some time to discount any further potential aetiologies.
- It was felt by the Board that this was warranted.

	- It was asked by the Ministry that the Board form a conclusion based on the current available evidence so that the Ministry can inform the public and family as soon as possible. - It was further highlighted by the Ministry that the final cause of death is to be decided by the pathologist and the coroner but the ISMB's position is to agree on the likely level of association between the vaccination and the death. - The Board agreed that this should be classified as probable.
4	Case 2 s 9(2)(a) [redacted] presentation and discussion *CARM described the circumstances of the case:* - CARM acknowledged the tragedy of this sudden death of a s 9(2)(a) [redacted] - s 18(c)(ii) [redacted] *The pathologist and registrar described their findings in the post-mortem:* - s 18(c)(ii) [redacted]

- s 18(c)(ii) [redacted]

Discussion:

- s 9(2)(g)(i), s 18(c)(ii) [redacted]

s 9(2)(g)(i), s 18(c)(ii)

[redacted]

5	Case 3 s 9(2)(a) presentation and discussion *CARM presented the case:* - s 18(c)(ii) [redacted] s 18(c)(ii) [redacted]
6	s 9(2)(g)(ii) and s 9(2)(g)(ii) *present the international evidence around aetiologies and presentation of myocarditis, the reporting of myocarditis within the New Zealand population, and the known cases of fatal myocarditis following Comirnaty from other regulators.* - The Board thanked Medsafe for their presentation - It was highlighted that the international evidence has found fatal cases, but these are only adequately identified following a post-mortem with histological examinations of the heart. - It was emphasised that there is no clear evidence that a change in interval between the two doses of Comirnaty reduces the likelihood of myocarditis following the second dose. - It was noted that a recent publication in Ontario that indicates evidence for a reduction in incidence following an increased interval is misleading given the data was presented in such a manner that a difference in incidence of myocarditis can easily be observed. - It was further agreed that there is no clear evidence of an association between dosing interval and incidence of myocarditis in New Zealand. It was also acknowledged that when looking at the effect of dosing interval in New Zealand it is likely to be confounded by the stage of the vaccine rollout, given we vaccinated young people after the return to a 3-week interval, while middle aged people were vaccinated during the 6-week interval recommendation, but considering young people are the at-risk group.
7	Summary and recommendations *Recommendations for the programme were made following the discussions of each case.* - s 18(c)(ii) [redacted] - s 9(2)(g)(i) [redacted]

- It was agreed by the Board that education about the risk of myocarditis is best done at the time of vaccination in a face-to-face manner.
- s 9(2)(g)(i) [redacted]
- It was noted that the communications must include more than just chest pain but also heart flutters and skipping beats to better reflect the diversity of cardiac symptoms experienced by patients with myocarditis.
- It was also asked by the Board that the communication includes a mention of the baseline rate of myocarditis in the population irrespective of vaccination and that some of these cases are fatal.
- It was asked by the pathologists that the communications also include mention of the risk of myocarditis following COVID-19 infection, which is significantly higher than the risk of myocarditis following vaccination, so that this should not deter people from receiving their vaccinations.
- The Board agreed to this point.
- It was asked by the pathologists that the communications also include mention of the risk of myocarditis following COVID-19 infection, which is significantly higher than the risk of myocarditis following vaccination, so that this should not deter people from receiving their vaccinations.
- The Board agreed to this point.
- It was also noted by the Board that there is data that suggests intravenous (IV) administration of the vaccine may be related to the development of myocarditis following mRNA vaccination.
- A study in mice that showed that only mice that received mRNA vaccine via the IV route developed myocarditis.
- s 9(2)(g)(i) [redacted]
- It was noted by the COVID-19 Vaccine and Immunisation Programme's (the CVIP) Strategic Communications manager that information to consumers at the time of vaccination is essential as there is substantial evidence that face-to-face communication is the most effective means of communication. It was acknowledged however that written communications already exist.
- s 18(c)(ii) [redacted]
- It was further noted by the Clinical Lead that while the written guidance is there, this is not necessarily reflected in verbal communication of the risk at time of vaccination.
- It was also noted by the Clinical Lead that the Programme is mindful of ensuring a better health system wide response to myocarditis, particularly frontline medical services like the emergency department and primary care, so that they are better alert to myocarditis being part of the differential. s 9(2)(g)(i) [redacted]
- It was asked by CARM that the Ministry ensures consistency in this messaging so that it is clear for consumers and that there is mindfulness around the possibility of information overload.
- It was asked by the Board that the communications also reflect that myocarditis, even when florid, is rare and treatable if detected early.
- The value of post-mortems following sudden death was also reiterated by members of the Board.

	CONCLUSION – Recommendations from CV-ISMB to the Ministry: - Generate communications that better mirror the cardiac symptoms experienced during myocarditis. - Implement changes in the Programme so that vaccinators alert individuals to the risks of myocarditis, with particular emphasis on at-risk groups such as young men. - Consider the implementation of aspiration during vaccination to ensure adequate IM vaccination during mRNA vaccinations. - Communicate that myocarditis following Comirnaty is the probable cause of the death of the s 9(2)(a) . - Communicate that s 18(c)(ii) is the possible cause of the death of the s 9(2)(a) , pending further information. - Communicate that myocarditis is likely the cause of death of the 62-year-old man but that this is unlikely to be related to the vaccination s 9(2)(a) - Communicate that the risk of myocarditis is rare and treatable with good outcomes when treatment is started quickly and should not deter people from vaccination, including a mention of the risk significantly more likely to occur following COVID-19 infection.
8	Karakia & Closing

Document 9

MINISTRY OF HEALTH
MANATŪ HAUORA

133 Molesworth Street
PO Box 5013
Wellington 6140
New Zealand
T+64 4 496 2000

14 January 2022

To whom it may concern

The COVID-19 Independent Safety Monitoring Board (CV-ISMB) works alongside the Centre for Adverse Reactions Monitoring (CARM) to assist with pharmacovigilance monitoring of COVID-19 vaccines. The CV-ISMB is a panel of experts from clinical medicine, biostatistics and microbiology that informs and supports CARM during assessments into the strength of association between a vaccination event and an adverse event following immunisation (AEFI).

A risk of myocarditis and pericarditis following vaccination with the Pfizer Comirnaty COVID-19 vaccine has been identified as a rare side effect and is well described in international literature. Myocarditis and pericarditis have been observed within the New Zealand population.

The CV-ISMB considers that in instances of sudden or unexplained deaths, in close temporal association to an mRNA COVID-19 vaccination, there is merit in proposing to the Coroner that a histopathological examination of the heart be considered. This may help the coronial investigation with understanding the potential role of vaccination. In the event that the Comirnaty vaccine may be involved please report the death to CARM.

Please note that the role of CARM and the CV-ISMB is to consider the strength of association between vaccination and a reported medical event. An investigation into the cause of death is under the authority of the Office of the Chief Coroner.

Yours sincerely

Dr Tim Hanlon
Group Manager Post Event
National Immunisation Programme

Document 10

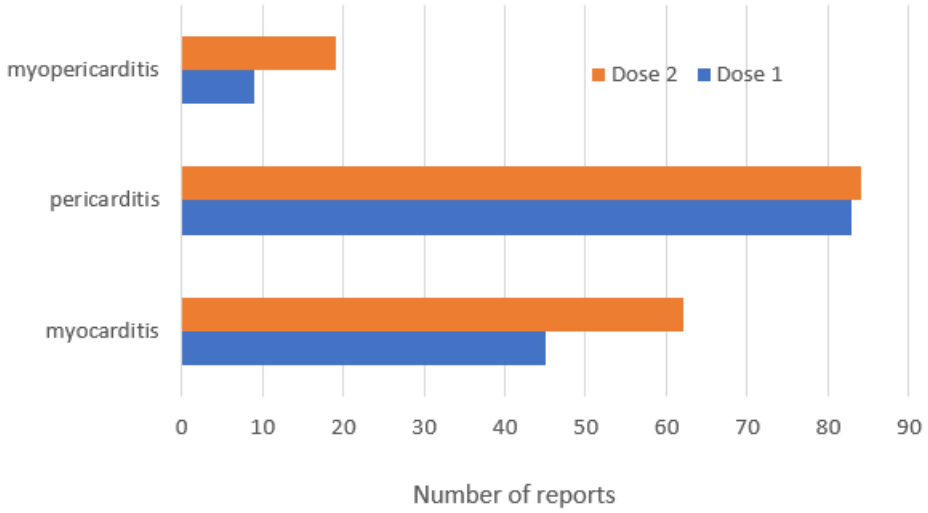
Update on reported cases of myocarditis/pericarditis/myopericarditis

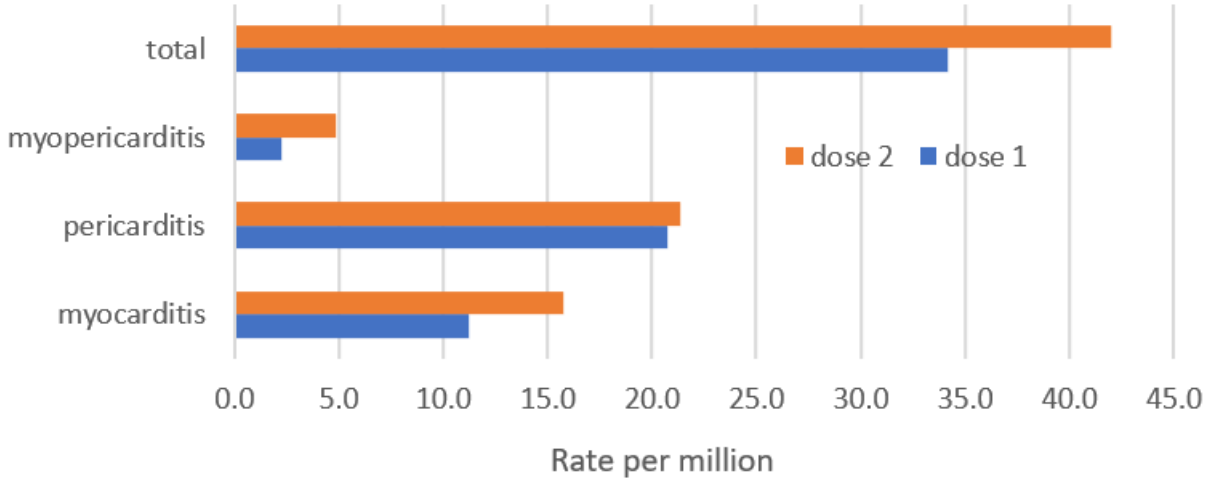
s 9(2)(g)(ii) [redacted]

9 February 2022

Document 10

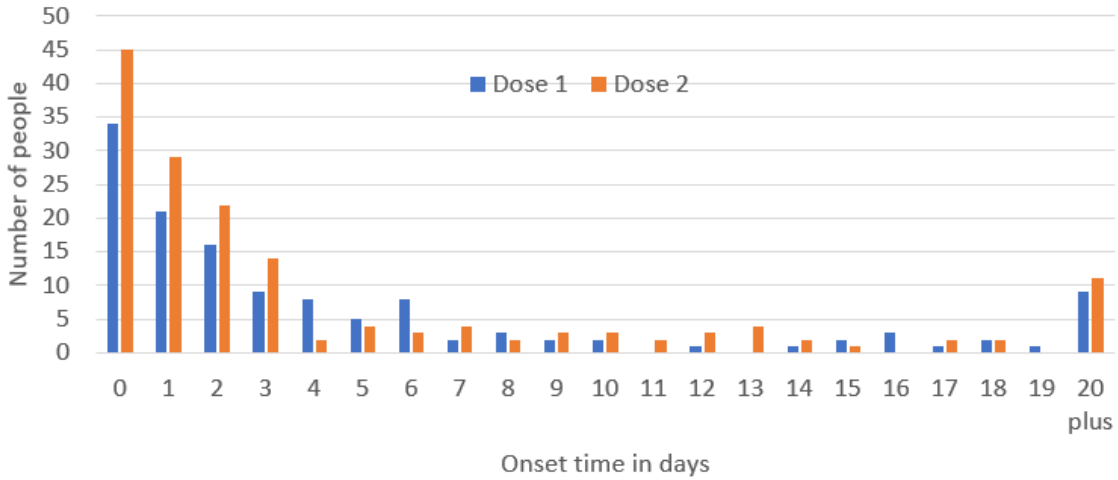
Diagnosis types

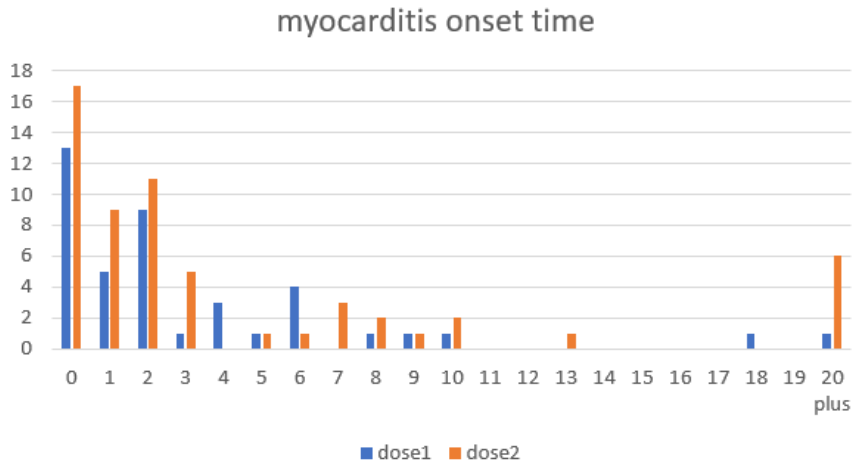




Document 10

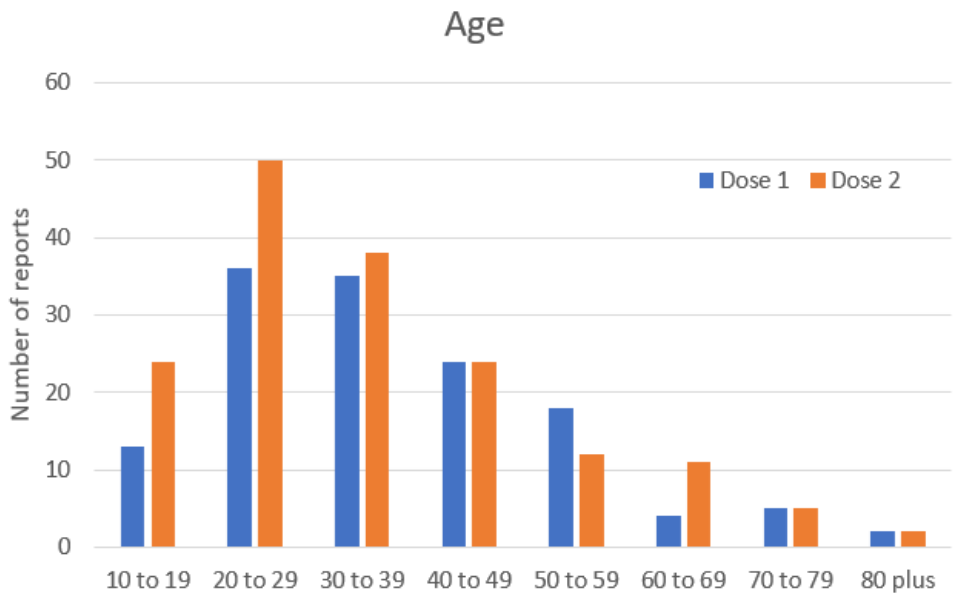
Onset time

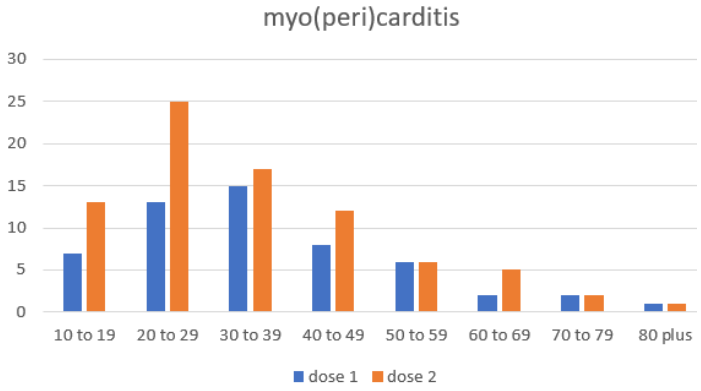


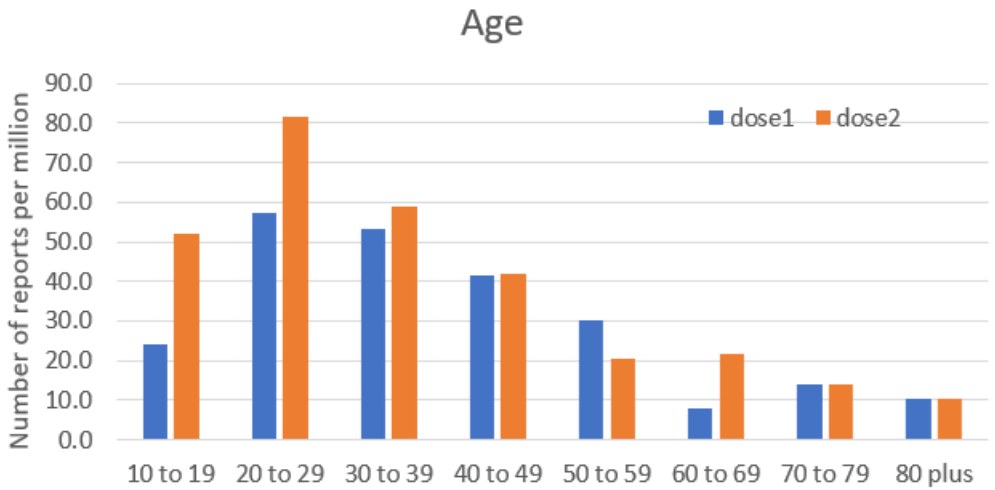


Document 10

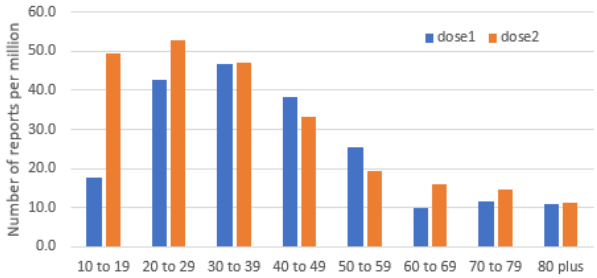
Age





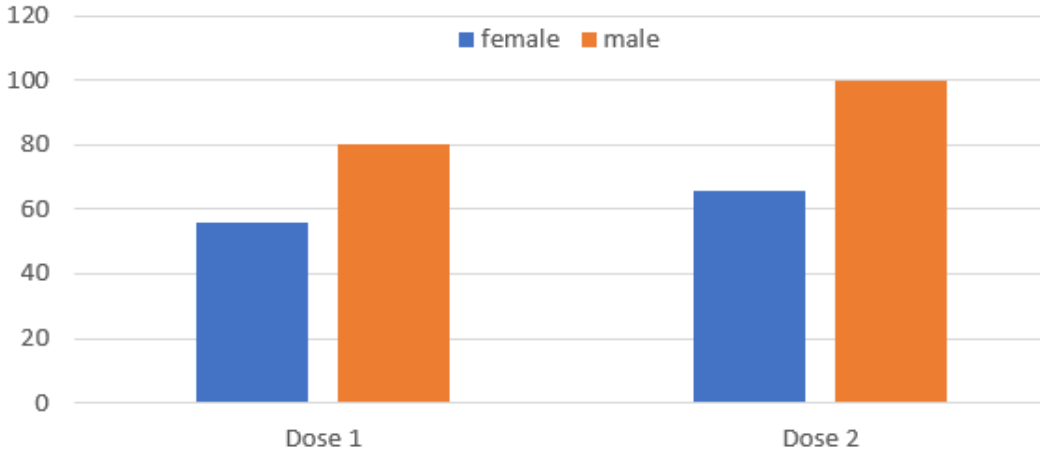


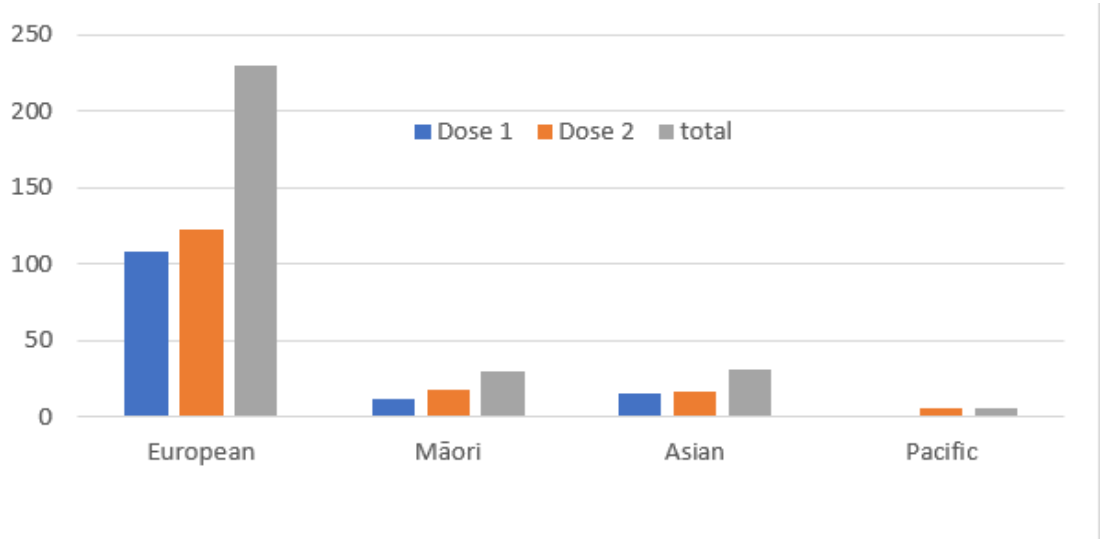
For comparison, early December 2021



Document 10

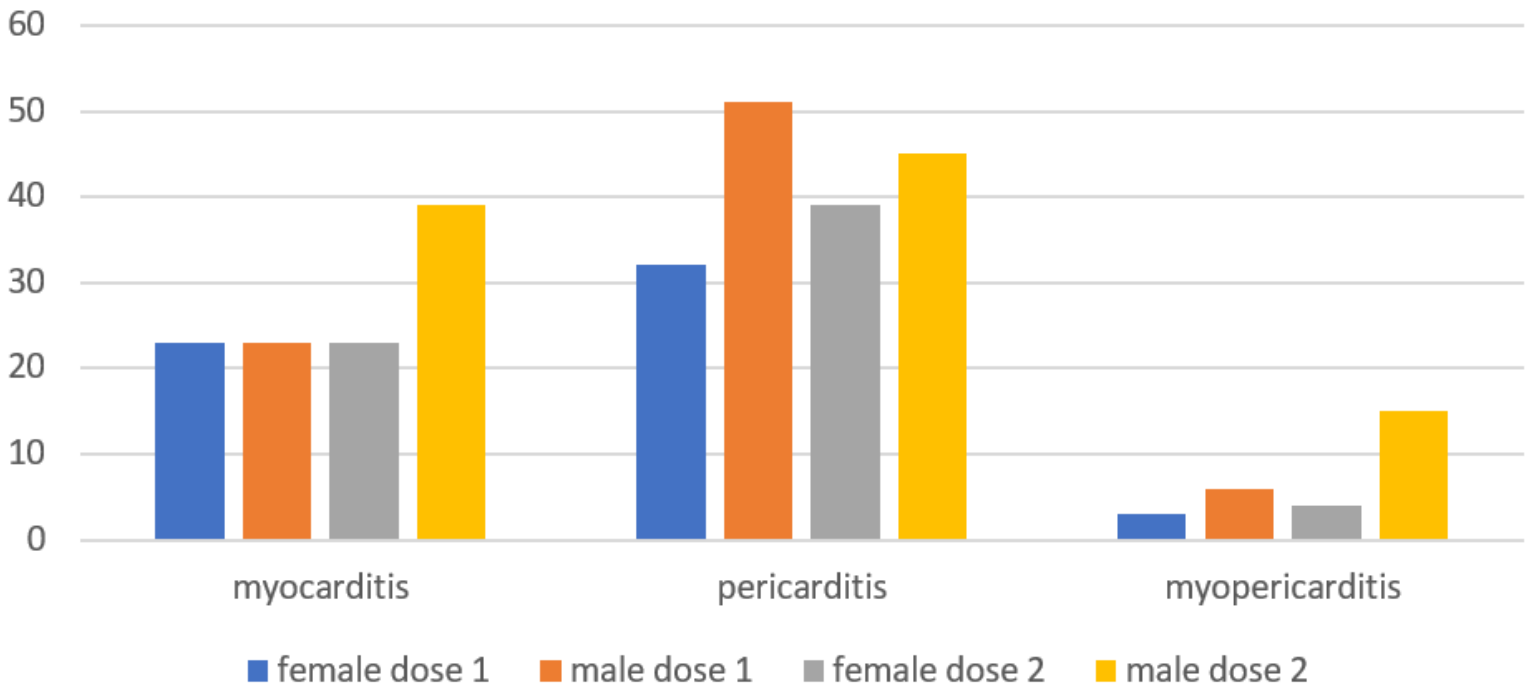
Gender and ethnicity





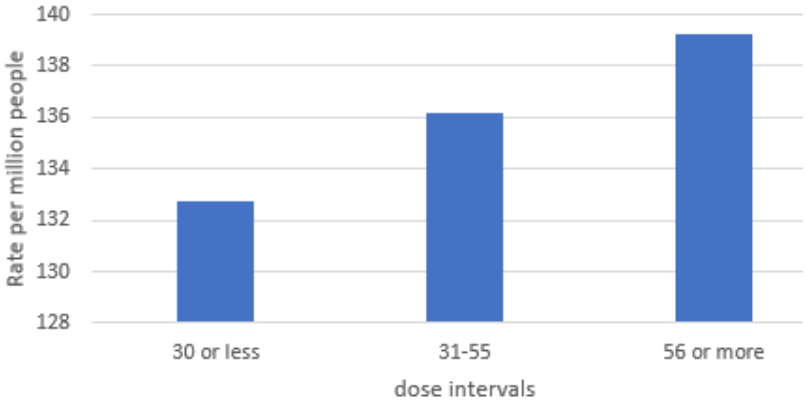
Document 10

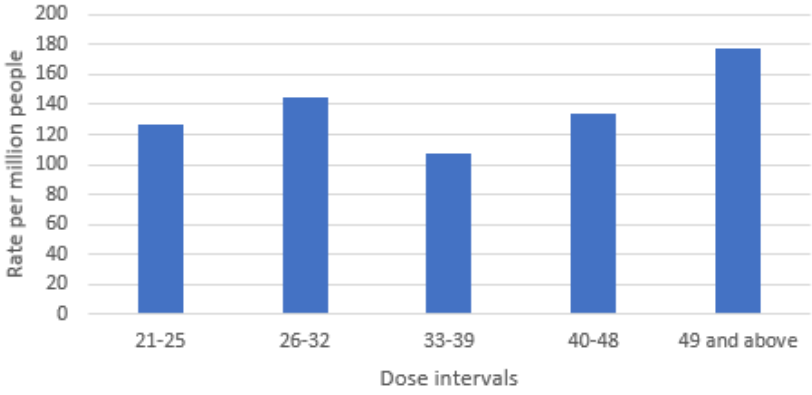
Diagnosis, dose and gender

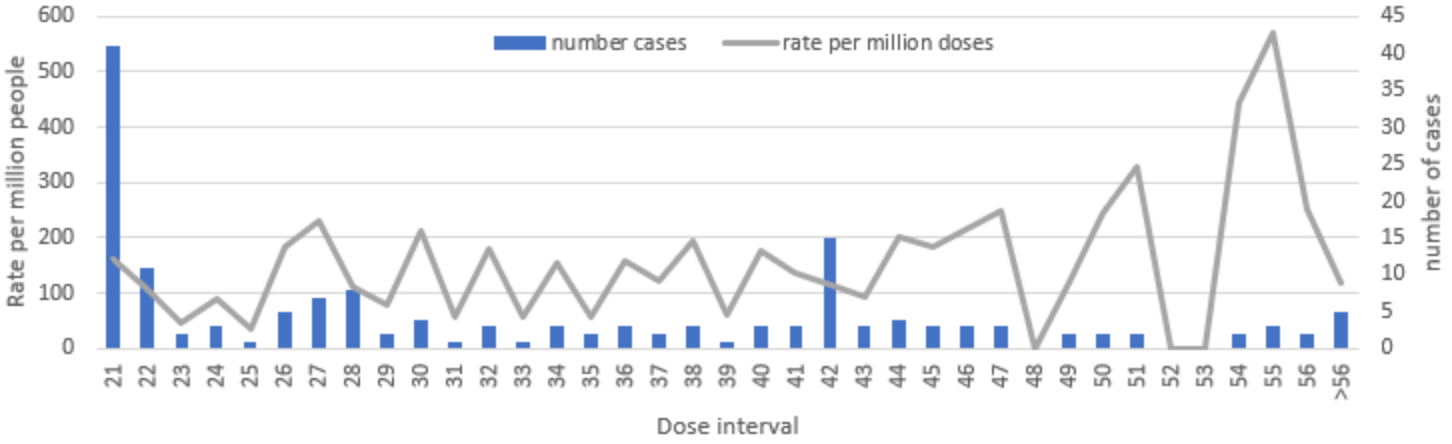


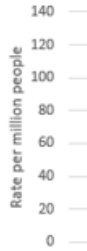
Document 10

Dose interval dose 1/2





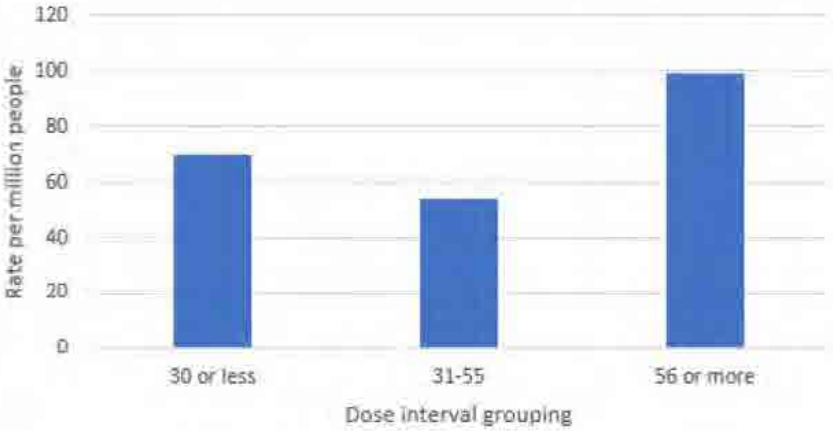


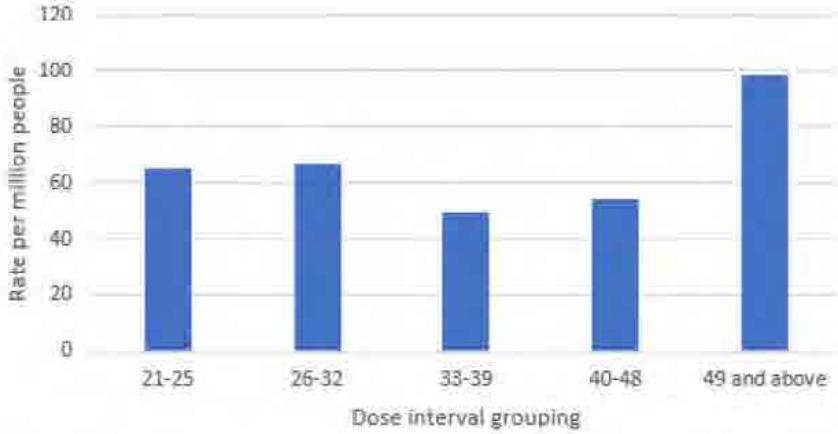


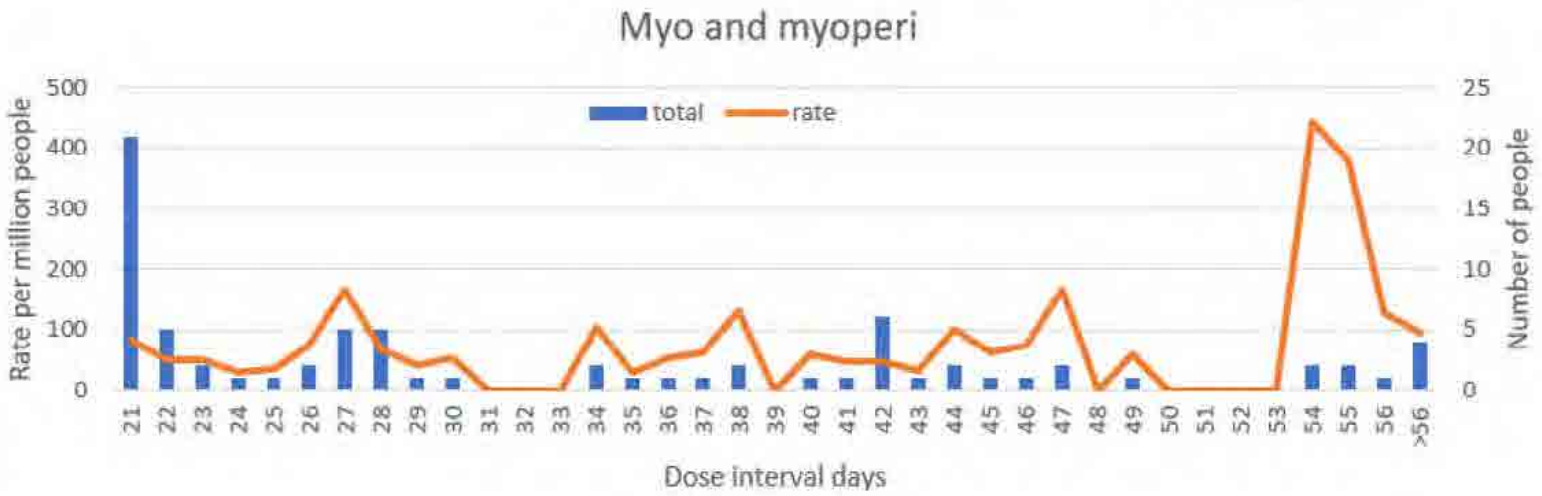
21 individuals reporting after dose 1 went on to have dose 2, no further report received.
10 individuals reporting after dose 2 went on to have dose 3, no further report received.

Document 19

Dose interval- myocarditis and myopericarditis







Minutes

MINISTRY OF HEALTH
MANATŪ HAUORA

Independent Safety Monitoring Board

Date:	02 March 2022
Time:	4.00-6.00pm
Location:	133 Molesworth Street, Wellington & Microsoft Teams
Chair:	Dr John Tait
Members:	Dr Hilary Longhurst, Dr Maryann Heather, Saskia Schuitemaker, Dr Nick Cutfield, Professor Thomas Lumley, Dr Owen Sinclair, Professor Ralph Stewart, Dr Tom Hills, Professor Chris Frampton, Associate Professor Matt Doogue, Professor Lisa Stamp, Dr Laura Young, Dr Wendy Hunter, Associate Professor Michael Tatley
Ministry of Health Attendees:	s 9(2)(g)(ii) [redacted]
Guests:	s 9(2)(a) [redacted]
Apologies:	Dr Enver Yousuf, Dr Kyle Eggleton, Dr Anja Werno
Secretariat Support:	s 9(2)(g)(ii) [redacted]

Item	Notes
1.	**Welcome and Karakia** • Meeting opened at 4:03 by the Chair • Karakia performed •
2.	**Minutes from last meeting** • Minutes from last meeting (9 February) accepted.
3.	**Update** • Update from the Chair about the presentation of the Interim report to CV-TAG, including concerns raised about inequitable rollout. All recommendations were accepted.
4.	s 18(c)(ii) [redacted]

Document 11

s 18(c)(ii)

[redacted]

Document 11

	s 18(c)(ii) [redacted]

Document 11

	s 18(c)(ii) [redacted]
5.	s 18(c)(ii) [redacted]

	s 18(c)(ii) [redacted]
6.	**Statistical Analysis of Safety Signal** *The Ministry gave an overview to the Board of the current safety signal investigation into thrombosis. The use of self-controlled case series design and the data sources were explained. The Ministry explained the potential safety signal raised for lower limb thrombosis, which was statistically significant, however noted the opposite finding for venous thrombosis which saw a statistically significant decrease in risk. When the two codes were combined, due to the similar classification, there was no signal. It was noted that Thrombosis had previously been presented to the ISMB and there was no clear information at that time to confirm a safety signal.* • A member of the Board noted that it was not clear exactly what events are included in venous thromboembolism compared to lower limb thrombosis codes. • Another member of the Board noted that lower limb deep vein thrombosis is the most common type of venous thromboembolism. Given the small number of cases with the lower limb thrombosis codes, she considered it likely that other cases of lower limb thrombosis had been coded as venous thromboembolism. Venous thromboembolism would also include conditions such as pulmonary embolism. This was the rationale for combining the codes, and this seems appropriate. They commented that the data was reassuring and in line with international data.

	• A member of the Board stated that coding variance can impact these types of analyses. It was noted that coding classifications are not the terms that are used clinically. • The Ministry asked the Board whether more analysis was required to investigate this possible safety signal. • A member of the Board suggested that the Ministry could do a chart review of a sample if the Board was concerned about a possible safety signal. They suggested it would be sufficient to sample lower limb thrombosis to get a better idea of what the clinical manifestation are (for example, deep vein thrombosis, phlebitis, or something unexpected). • It was noted that the lower limb thrombosis code may include conditions such as superficial thrombophlebitis. • A member said it would be concerning if there was a safety signal for deep vein thrombosis as opposed to superficial thrombophlebitis which would be less of a concern. • A member of the Board noted that chart reviews are a significant undertaking, and she was not convinced that there was reason to do this. • Several members of the Board agreed they were not concerned by the data. • There were no objections.
7.	**AOB** • The Board was reminded that there would be a meeting on 09 March.
9	**Closing** • A karakia was performed. • The meeting closed at 5.59pm.

Document 12

Memo

Date:	23 March 2022		
To:	s 9(2)(g)(ii) Manager, Clinical Risk Management, Medsafe		
From:	s 9(2)(g)(ii), Clinical Risk Management		
Subject:	**The safety of COVID-19 vaccination during pregnancy**		
Incident ID:	28963	**Lotus Notes Location:**	**Immunological Products & Vaccines – CV-ISMB**
For your:	Action: [√]	Decision: [√]	Information: [√]

DESCRIPTION

This memo summarises the available information on safety and pregnancy outcomes when COVID-19 vaccines are administered during pregnancy. This memo covers new information that has become available since the last memo dated 22 October 2021 (Annex 1). This information largely relates to mRNA vaccines, including Comirnaty, which is the recommended vaccine for use during pregnancy in New Zealand [1].

NATURE OF THE SAFETY CONCERN

Vaccination during pregnancy

Vaccine-preventable diseases can be associated with significant morbidity and mortality in pregnant people, fetuses, and neonates. In some cases, immune system changes during pregnancy can increase the susceptibility of the pregnant person and fetus to certain infectious diseases and increase the risk of serious outcomes. Vaccination can provide direct protection of pregnant women, and can also protect the fetus and infant through placental transfer of antibodies during pregnancy. COVID-19 vaccination is known to be effective in the protection of pregnant women from COVID-19 disease. Placental transfer of antibodies against SARS-CoV-2 has also been demonstrated [1-3].

There are no safety concerns surrounding administration of non-live vaccines during pregnancy. Caution around administration of live attenuated vaccines such as the measles, mumps and rubella (MMR) vaccine is based on the theoretical risk of placental transfer of attenuated virus and subsequent infection of the foetus. However, evidence of foetal harm after vaccination has not been identified. A review of the evidence around safety of vaccination during pregnancy by the Global Advisory Committee on Vaccine Safety found no safety concerns with influenza, tetanus toxoid, meningococcal, MMR, poliovirus or yellow fever vaccines [1, 2]. There is international consensus that evidence indicates there are no pregnancy safety concerns with COVID-19 vaccines (see section on recommendations from local and international bodies.

Risks of COVID-19 disease during pregnancy

The New Zealand immunisation handbook states:

> *'Although pregnant women are not at increased risk of SARS-CoV-2 infection, they are at increased risk of severe disease and death compared with age-matched non-pregnant women. While the absolute risk of severe outcomes among pregnant women is low compared with absolute risk due to advanced age, the risk of hospital admissions is three times higher and the rate of ICU care for COVID-19 has been found to be five times higher (relative risk 5.04; 95% CI 3.13–8.10) for pregnant women than for non-pregnant women. Obesity, hypertension, asthma, autoimmune disease, diabetes and older age are also associated with severe COVID-19 in pregnant women.*
>
> *Infants of mothers with COVID-19 are at increased risk of preterm birth, particularly due to early delivery, and neonatal ICU admission.[49, 52] Early studies do not suggest intrauterine transmission, but transmission during birth has been shown in around 3 percent of neonates. Most neonatal infections are asymptomatic or mild, but around 12 percent experience severe disease with dyspnoea and fever as the most commonly reported signs.'*

Spontaneous abortion and stillbirth

Spontaneous abortion or miscarriage is a non-viable pregnancy up to 20 weeks gestation. Most commonly, this occurs during the first trimester, which is referred to as early pregnancy loss. Second trimester pregnancy loss occurs after 13 and before 20 weeks gestation and still-birth refers to pregnancy loss at 20 weeks gestation or later [4].

The true incidence of early pregnancy loss is difficult to ascertain as many losses occur before the pregnancy is clinically recognised. The incidence of spontaneous abortion is thought to be around 20% of clinically recognised pregnancies, but has been estimated to be as high as 31% of all pregnancies based on logistic regression.

There are more than 2,000 hospitalisations in New Zealand each year for spontaneous abortions. Most people who experience a miscarriage do not require an inpatient stay in hospital, so this is a significant undercount of the true number of people experiencing spontaneous abortion. In addition, many people may miscarry without knowing they were pregnant. For these reasons, the total number of miscarriages each year in New Zealand cannot be identified.

The risk of pregnancy loss changes with age. One study found rates of early pregnancy loss of 17 percent (<20 years), 11 percent (20 to 24 years), 10 percent (25-29 years), 11 percent (30 to 34 years), 17 percent (35 to 39 years), and 33 percent (40 to 44 years). Other risk factors for pregnancy loss include prior pregnancy loss, diabetes, obesity, thyroid disease, stress, use of certain medicines and substance use. Some infections have been associated with increased risk of spontaneous abortion, although the mechanism for this is unclear [4, 5].

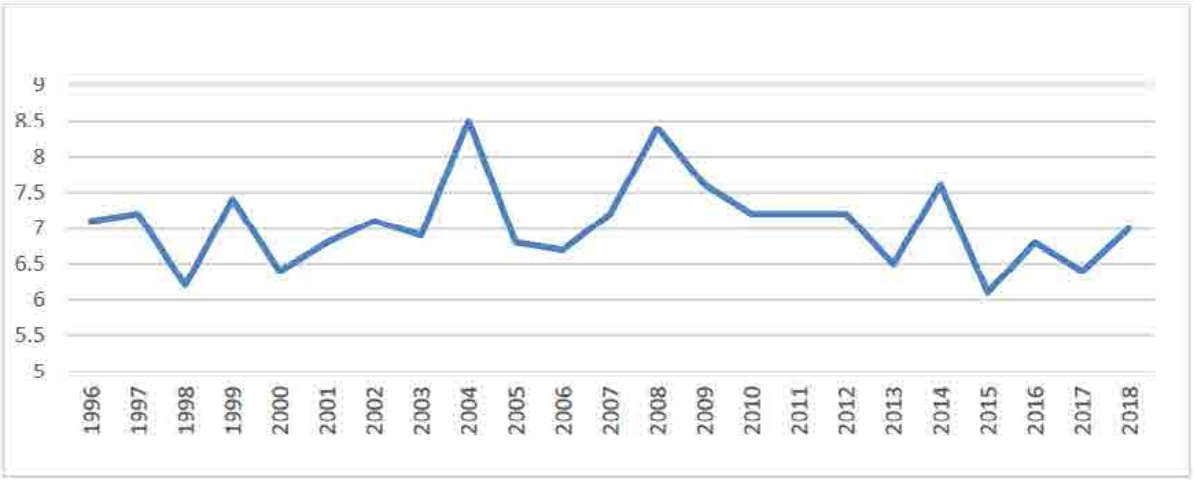
Chromosomal abnormalities, maternal anatomic abnormalities and significant trauma may also cause pregnancy loss. There can be multiple factors involved in second trimester pregnancy loss and often no cause is identified [4].

The cause of a stillbirth is often unknown. Congenital abnormalities, fetal growth restriction, infection, genetic abnormalities, hydrops fetalis, fetal arrhythmia, abruptio placentae, umbilical cord abnormalities, placental abnormalities and fetomaternal haemorrhage are known causes of stillbirth [6].

Sociodemographic risk factors for stillbirth include younger or older maternal age, nulliparity, parity >3 and severe deprivation. Previous stillbirth or adverse pregnancy outcome, diabetes, hypertension, substance abuse and obesity are also risk factors [6].

The rates of stillbirth in New Zealand vary from year to year and by demographic. There were 414 stillbirths in 2018, which equates to an overall rate of 7.0 per 1000 total births. The number of fetal and infant deaths in New Zealand is small and causes rates to fluctuate markedly from year to year. As the rates in figure 1 are derived from small numbers, they should be interpreted with caution.

Figure 1: Rates of stillbirth, 1996-2018



Source: New Zealand Mortality Collection via the Fetal and Infant Deaths Web Tool (accessed 1 March 2022). Note: Fetal death rates are expressed as per 1000 total births. Fetal deaths presented in this publication only include those meeting the definition of a stillbirth (weighing ≥400 g birthweight or who were ≥20 weeks gestation at birth). This includes deaths resulting from terminations of pregnancy.

PRODUCTS

Product name	Sponsor	TT50
Comirnaty*	Pfizer New Zealand Limited	10853

*Comirnaty is the only vaccine currently recommended for use during pregnancy in New Zealand.

INDICATIONS

Comirnaty is currently the only vaccine recommended for use during pregnancy in New Zealand. The adult formulation of Comirnaty has provisional consent for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV2, in individuals 12 years of age and older. The use of this vaccine should be in accordance with official recommendations.

INFORMATION IN LOCAL AND INTERNATIONAL PRODUCT INFORMATION

Section 4.6 of the New Zealand data sheet includes the following information relating to use in pregnancy:

> *'There is limited experience with use of COMIRNATY in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition or post-natal development (see Fertility). Administration of COMIRNATY in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and fetus.'*

The United Kingdom summary of product characteristics and Australian product information are identical to the New Zealand data sheet.

The Canadian product monograph states:

> *'The safety and efficacy of COMIRNATY in pregnant women have not yet been established. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/ fetal development, parturition, or post-natal development.'*

The United States prescribing information states:

> *'There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to COMIRNATY during pregnancy. Women who are vaccinated with COMIRNATY during pregnancy are encouraged to enrol in the registry by visiting https://mothertobaby.org/ongoing-study/covid19-vaccines/.*
>
> *Risk Summary*
>
> *All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Available data on COMIRNATY administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.*
>
> *A developmental toxicity study has been performed in female rats administered the equivalent of a single human dose of COMIRNATY on 4 occasions; twice prior to mating and twice during gestation. These studies revealed no evidence of harm to the fetus due to the vaccine.*
>
> *Animal Data*
>
> *In a developmental toxicity study, 0.06 mL of a vaccine formulation containing the same quantity of nucleoside-modified messenger ribonucleic acid (mRNA) (30 mcg) and other ingredients included in a single human dose of COMIRNATY was administered to female rats by the intramuscular route on 4 occasions: 21 and 14 days prior to mating, and on gestation days 9 and 20. No vaccine-related adverse effects on female fertility, fetal development, or postnatal development were reported in the study.'*

SOURCE OF SAFETY CONCERN

Review of safety data regarding vaccination during pregnancy is part of routine pharmacovigilance activities. There have been reports of AEFIs after vaccination during pregnancy (see section on spontaneous reporting data in New Zealand) and there is considerable public interest in the safety profile during pregnancy.

REVIEW OF THE AVAILABLE INFORMATION

Spontaneous reporting data in New Zealand

General reporting patterns

As of 22 March 2022, there were a total of 60,378 cases in the database of which 569 had the pregnancy checkbox selected by the reporter. When restricted to females aged 16-49 years, 462 report remain (67 serious). All reports were for Comirnaty, aside from one case for Vaxzevria. The total number of people that have been vaccinated during pregnancy is unknown, as this information is not recorded at the point of vaccination.

The overall spontaneous reporting trends for cases marked as pregnant are similar to those for the general population. Figure 2 shows the top reported terms for cases marked as pregnant in females

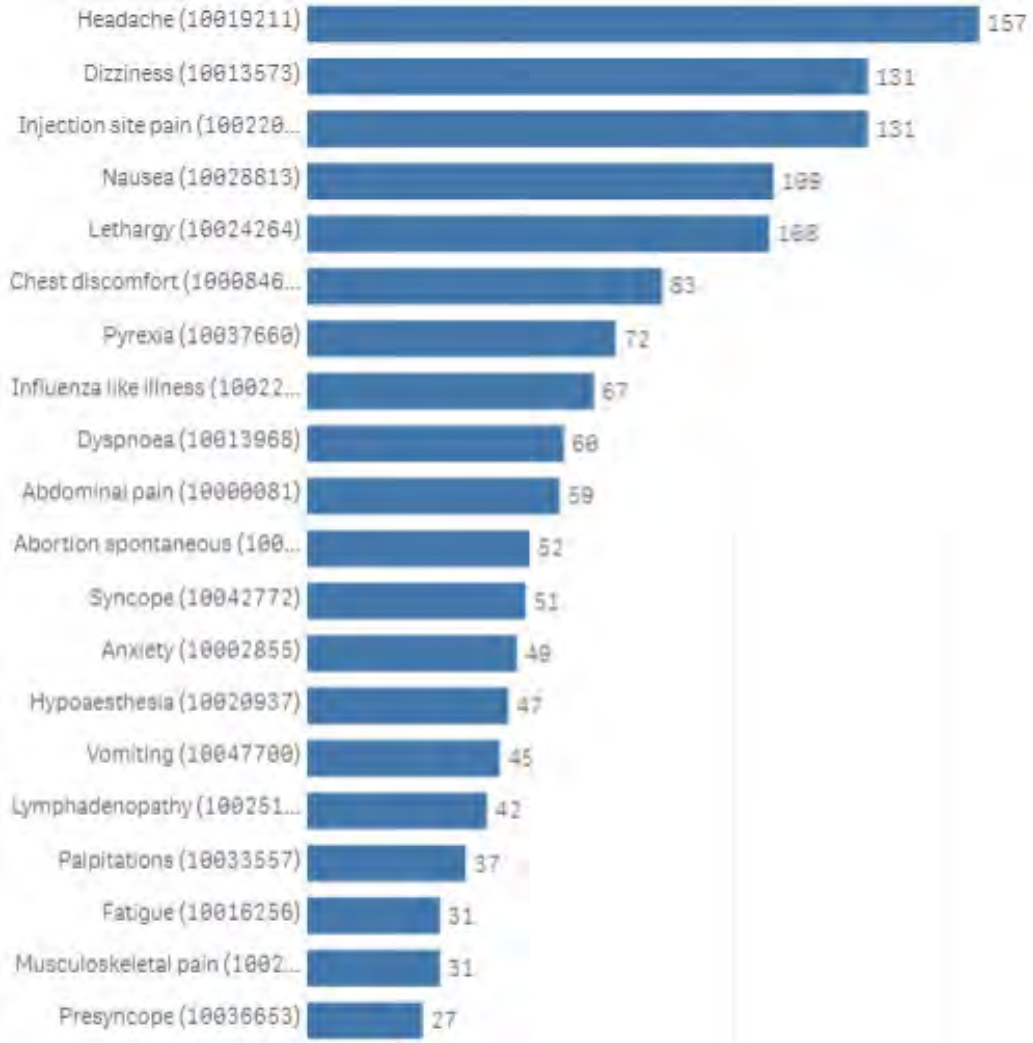
aged 16-49 years, which are also frequently reported in the overall population, with the exception of spontaneous abortion.

Table 1 compares the proportion of these cases reporting each term and compares this to the overall population. The proportion of cases reporting each term is similar between the pregnant cases and general population. Reporting rates were unable to be calculated as the total number of doses administered to pregnant people is unknown.

When compared to overall reports, it appears that a higher proportion of the pregnant cases reported vomiting (9.7% vs 5.1%) and abdominal pain (12.8% vs 7.7%). Conversely, a lower proportion of pregnant cases appeared to report lymphadenopathy (9.1% vs 11.9%). These differences are small and highly uncertain due to the limitations of passive reporting. However, the terms reported and general patterns are consistent with international experience and the literature, and do not highlight any safety concerns.

Figures 3 and 4 show the age and ethnicity of pregnant cases.

Figure 2: Most frequently reported adverse report terms for cases marked as pregnant in females aged 16-49 years



Source: COVID-19 Adverse Events Following Immunisation Qlik app, updated 22 March 2022 (accessed 22 March 2022).

Table 1: Proportion of cases reporting the most frequent AEFI terms for cases marked as pregnant in females aged 16-49 years, compared with the overall population

AEFI term	**Percentage of pregnant cases reporting AEFI**	**Percentage of all cases reporting AEFI**
Headache	34.0%	31.2%
Dizziness	28.4%	29.3%
Injection site pain	28.4%	25.6%
Nausea	23.6%	21.1%
Lethargy	23.4%	24.4%
Chest discomfort	18.0%	20.3%
Pyrexia	15.6%	14.4%
Influenza like illness	14.5%	13.7%
Dyspnoea	13.0%	11.7%
Abdominal pain	12.8%	7.7%
Abortion spontaneous*	11.3%	n/a
Syncope	11.0%	9.4%
Anxiety	10.6%	8.5%
Hypoaesthesia	10.2%	9.9%
Vomiting	9.7%	5.1%
Lymphadenopathy	9.1%	11.9%
Palpitations	8.0%	7.8%
Fatigue	6.7%	4.7%
Musculoskeletal pain	6.7%	6.0%
Presyncope	5.8%	4.9%

Source: COVID-19 Adverse Events Following Immunisation Qlik app, updated 22 March 2022 (accessed 22 March 2022).

*Note that there are additional cases of spontaneous abortion that are not marked as pregnant.

Figure 3: Age groups of pregnant cases

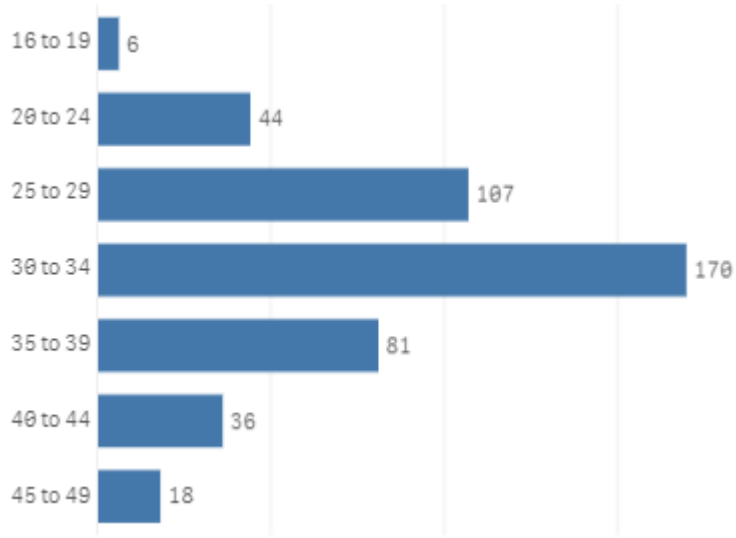
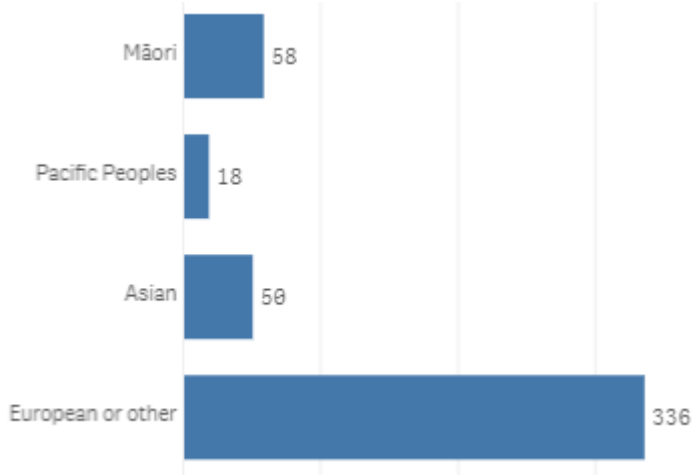


Figure 4: Ethnicity of pregnant cases



Serious cases

The terms reported for the 67 serious cases were spontaneous abortion (41), chest discomfort (12), abdominal pain (11), headache (11), dyspnoea (10), anxiety (9), dizziness (9), lethargy (8), injection site pain (7), nausea (7), pyrexia (7), syncope (7), vaginal haemorrhage (7), hypoaesthesia (6), presyncope (5) influenza like illness (4) palpitations (4), fatigue (3), insomnia (3), menstrual disorder (3), premature labour (3), pulmonary embolism (3), rash (3), tachycardia (3), vomiting (3), wheezing (3), abortion missed (2), disturbance in attention (2), exposure during pregnancy (2), oedema peripheral (2), paraesthesia (2), rash erythematous (2) rash pruritic (2), stillbirth (2), swelling (2), vision blurred (2), weight decreased (2), abortion (1), ageusia (1), alopecia areata (1), arthralgia (1), bronchospasm (1), congenital anomaly (1), decreased appetite (1), depressed level of consciousness (1), erythema multiforme (1), face oedema (1), feeling of body temperature change (1), haemorrhage (1), hypokinesia (1), injection site paraesthesia (1), injection site pruritus (1), lymphadenopathy (1), musculoskeletal pain (1), myalgia (1), nephrotic syndrome (1), periorbital oedema (1), photophobia (1),

pruritus (1), restlessness (1), seizure (1), sleep disorder (1), suicide attempt (1), superficial vein thrombosis (1), throat tightness (1), tinnitus (1), urticaria (1), vertigo (1).

It should be noted that these terms include those selected by the reporter and may not be medically confirmed.

Cases reporting pregnancy loss

As of 22 March 2022, there were 66 reports coded with the terms spontaneous abortion, abortion or missed abortion and two cases coded with stillbirth. There are also three reports of fetal hypokinesia and one report of congenital abnormality, which was included in the October 2021 memo. The details of the cases are provided in Annex 2.

Of the 66 cases reporting spontaneous abortion, abortion or missed abortion, 49 occurred in the first trimester, 5 occurred in the second trimester and 12 occurred at unknown gestation or stated early pregnancy. The two cases of stillbirth occurred at 29 and 39 weeks. Figures 5 and 6 show the age and ethnicity of the reported cases of pregnancy loss.

Figure 5: Age of cases reporting pregnancy loss

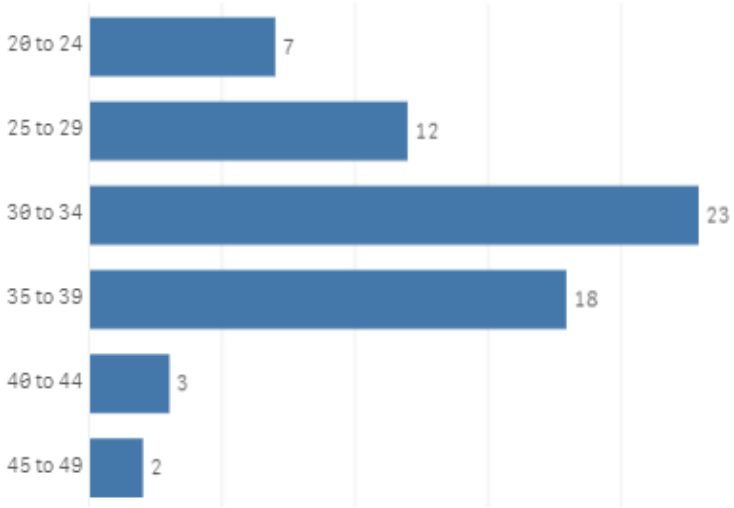
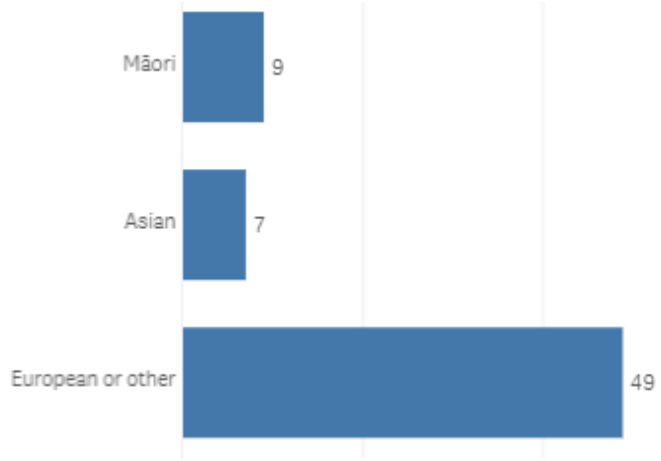


Figure 6: Ethnicity of cases reporting pregnancy loss

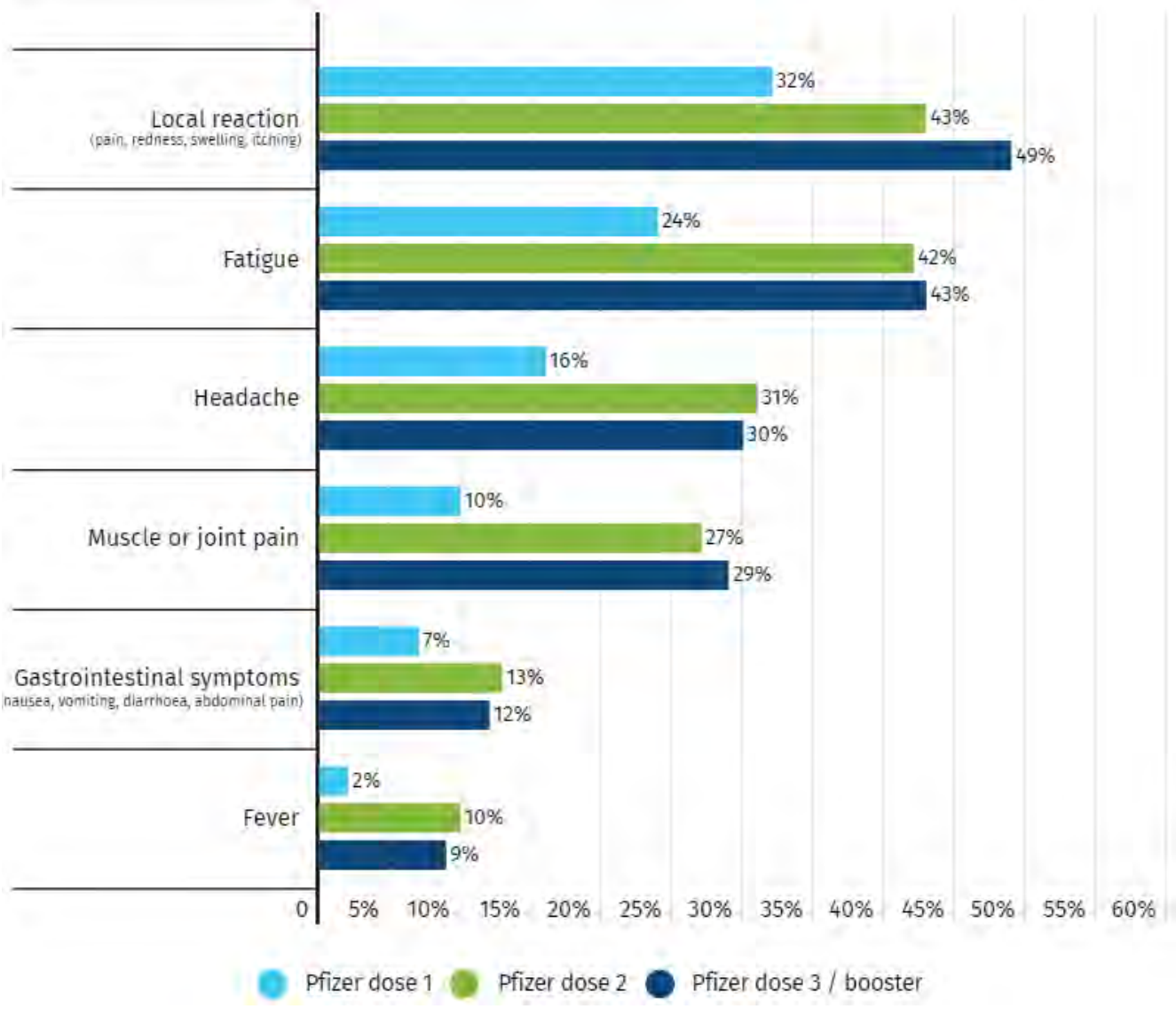


Solicited reporting in Australia

Australia has published results from AusVaxSafety, an active surveillance programme that includes COVID-19 vaccines. Information on adverse events is collected with surveys sent by text message or email at day three, day eight and six weeks after vaccination. Data from surveys completed by pregnant people at day 3 after vaccination with Comirnaty is summarised on the AusVaxSafety website.

As of 21 March 2022, there were 11,182 surveys completed after dose one, 12,118 surveys after dose two and 6,480 surveys after dose three. After doses one, two and three, 37%, 52% and 55% of respondents, respectively, reported at least one adverse event. Figure 7 shows the most frequently reported adverse events. Up to 2% of respondents reported seeking medical attention and up to 23% reported disruption of routine activities after each dose. People who presented to GPs and emergency departments had similar adverse events to those who didn't. Most people who reported disruption of routine activities had lethargy, headache and joint pain.

Figure 7: Frequently reported adverse events reported by pregnant participants at day three following vaccination with Comirnaty. AusVaxSafety, 2022 [7]



Recommendations from local and international bodies

The New Zealand Ministry of Health, COVID-19 Vaccine Independent Safety Monitoring Board, Royal Australian and New Zealand College of Obstetricians and Gynaecologists, Royal College of Obstetricians and Gynaecologists (UK), Joint Committee on Vaccination and Immunisation (UK), Canadian Ministry of Health, Centres for Disease Control and Prevention and European Medicines Agency have published communications in support of the safety of routine COVID-19 vaccination in pregnant people [8-13].

The WHO Strategic Advisory Group of Experts on Immunization (SAGE) recommends that pregnant people who are not already vaccinated against COVID-19 should have access to COVID-19 vaccination, because of the increased risk of severe illness and preterm birth. The WHO considers that the benefits of vaccination during pregnancy outweigh potential risks whenever there is ongoing or anticipated community transmission of the virus [3].

Table 2: WHO SAGE interim recommendations on vaccination during pregnancy [3]

WHO SAGE interim recommendations	Pfizer–BioNTech BNT162b2	Moderna mRNA-1273	AstraZeneca AZD1222	Janssen Ad26.COV2.S	Sinopharm BIBP	Sinovac–CoronaVac	Bharat Biotech BBV152	Novavax NVX-Co2373
Can pregnant women receive the vaccine?	✓	✓	✓	✓	✓	✓	✓	✓ *

*Because of the limited experience with the MatrixMTM adjuvant of the Novavax NVX-Co2373 vaccine in pregnancy, the benefit-risk assessment for this vaccine includes considering whether any other WHO EUL COVID-19 vaccine with a more established safety record in pregnancy is locally available.

Literature

In the previous memo on this topic, dated 22 October 2021, the available literature on COVID-19 vaccine safety and pregnancy outcomes after vaccination was summarised.

Shimabukuro et al examined data from the CDC v-safe COVID-19 Vaccine Pregnancy Registry and found the proportions of pregnancies with preterm birth or being small for gestational age at birth were consistent with background rates [14]. Blakeway et al found no difference between vaccinated and unvaccinated people for a range of adverse pregnancy outcomes [15]. Theiler et al and Trostle et al found no increased risk of maternal, pregnancy or delivery complications after vaccination [16, 17].

Kharbanda et al found that among women with spontaneous abortions, the odds of COVID-19 vaccine exposure were not increased in the prior 28 days compared with women with ongoing pregnancies [18]. Zauche et al found that the risk of spontaneous abortion after mRNA Covid-19 is consistent with the expected background risk [19].

Bookstein et al and Kachikis et al found that the short-term safety profile following vaccination is comparable to non-pregnant people [20, 21].

Relevant literature identified since the previous memo dated 22 October 2021 is summarised below. Most of the literature relating to pregnancy outcomes after vaccination includes participants predominantly vaccinated during the second or third trimester. Further accrual of follow-up time is needed to observe large numbers of pregnancy outcomes in people vaccinated during the first trimester. However, the first trimester data that exist do not raise any safety concerns.

New studies have also been published on fertility and the general safety profile in pregnancy.

Literature on pregnancy outcomes

Magnus et al, 2021. COVID-19 vaccination during pregnancy and first-trimester miscarriage [22]

This case control study, summarised in a letter to the editor, estimated the odds of COVID-19 vaccination in people who had first trimester miscarriage (cases) compared with people with a primary care confirmation of ongoing pregnancy in the first trimester (controls).

The data was derived from Norwegian registries and all registrations of first trimester miscarriages or ongoing first trimester pregnancies between 15 February 2021 and 15 August 2021 were identified. At the time of the study, vaccination during pregnancy was not recommended in Norway during the first trimester except in people underlying health conditions and the proportion of vaccinated people in the study was small (around 5%).

The authors estimated odds ratios for COVID-19 vaccination within 5-week and 3-week windows before a miscarriage or confirmed ongoing pregnancy. Adjustments were made for age, country of birth, marital status, educational level, household income, number of children, employment in a health care profession, underlying risk conditions for COVID-19, previous positive test for SARS-CoV-2, and calendar month.

There were 13,956 ongoing pregnancies (5.5% vaccinated) and 4,521 miscarriages (5.1% vaccinated) identified. For people who miscarried, the adjusted odds ratios were 0.91 (95% CI: 0.75 to 1.10) for vaccination within the prior three weeks and 0.81 (95% CI: 0.69 to 0.95) for vaccination within the prior five weeks (Table 5). Separate analyses were conducted with similar results for different vaccines, health care workers, and confirmed pregnancies with at least eight weeks of follow up to exclude subsequent pregnancy loss. The study did not find an association between COVID-19 vaccination and early pregnancy loss.

Table 3: Odds ratios for COVID-19 vaccination in a 5-week or 3-week window before miscarriage or confirmation of an ongoing pregnancy. Magnus et al, 2021 [22]

Vaccination Status	5-Week Exposure Window				3-Week Exposure Window			
	Ongoing Pregnancies	Miscarriages	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)*	Ongoing Pregnancies	Miscarriages	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)*
	number				*number*			
Among all women								
Unvaccinated	13,184	4,290	Reference	Reference	13,507	4,375	Reference	Reference
Vaccinated	772	231	0.92 (0.79–1.07)	0.81 (0.69–0.95)	449	146	1.00 (0.83–1.21)	0.91 (0.75–1.10)
Among health care personnel								
Unvaccinated	2,419	756	Reference	Reference	2,533	788	Reference	Reference
Vaccinated	261	75	0.92 (0.70–1.20)	0.93 (0.70–1.22)	147	43	0.94 (0.66–1.33)	0.92 (0.64–1.32)

* The odds ratios among all women were adjusted for age, country of birth, marital status, educational level, household income, number of children, employment in a health care profession, underlying risk conditions for coronavirus disease 2019 (Covid-19), and previous test positive for severe acute respiratory syndrome coronavirus 2. The odds ratios among health care personnel were adjusted for the same variables as among all women except for employment in a health care profession.

One limitation of the study was the inability to match for gestational age at registration, although the authors considered that most recognised miscarriages occur between weeks six and ten of pregnancy, which is similar to the period in which most pregnancies are confirmed in primary care. Other limitations were that many people in Norway do not have a primary care appointment to confirm pregnancy and some miscarriages are not clinically recognised.

Wainstock et al, 2021. Prenatal maternal COVID-19 vaccination and pregnancy outcomes [23]

This single-centre retrospective cohort study compared the odds of various pregnancy and neonatal outcomes between people vaccinated with Comirnaty and unvaccinated people. The study included all women who delivered live babies between January and June 2021 at Soroka University Medical Center, Israel. People with previous SARS-CoV-2 infection, multiple gestations or unknown vaccination

status or incomplete pregnancy follow up information were excluded. All vaccinations occurred during the third trimester.

The final study population included 913 vaccinated people and 3,486 unvaccinated people (before or during pregnancy). Vaccinated women were older, more likely to receive fertility treatment, less likely to receive insufficient prenatal care and had higher socioeconomic status.

A multivariate analysis was conducted that adjusted for maternal age, fertility treatments and socioeconomic score (table 6). No adverse associations were found between third trimester vaccination and any of the pregnancy or neonatal complications.

Table 4: Multivariable models for the association between vaccination and pregnancy, delivery and newborn characteristics and complications. Wainstock et al , 2021 [23]

Outcomes	**Adjusted Odds ratio* (vaccinated vs. unvaccinated); 95% CI**
Pregnancy complications diagnosed in late pregnancy	
Pregnancy related hypertensive disorders	1.13; 0.78–1.62
Oligohydramnios	0.84; 0.52–1.40
Polyhydramnios	0.77; 0.29–2.03
Pathological presentation	0.96; 0.63–1.48
Meconium stained amniotic fluid	0.52; 0.32–0.83
Delivery and post-partum characteristics	
Gestational age at delivery	β = −0.07; (−0.26–0.11)
Non reassuring fetal monitoring	0.70; 0.48–1.01
Caesarean delivery	0.93; 0.75–1.16
Vacuum delivery	0.99; 0.63–1.57
Postpartum haemorrhage	1.46; 0.63–3.38
Maternal postpartum fever	0.73; 0.15–3.51
Newborn characteristics	
Birthweight, gr. (mean ± SD)	β = −9.14; (−55–37.5)
Small for gestational age	0.79; 0.48–1.31
Newborn postpartum fever	1.45; 0.26–8.11
Newborn respiratory complications	0.88; 0.44–1.79

*All models adjusted for maternal age, fertility treatments and socioeconomic score

The authors noted that the study was insufficiently powered to detect differences between exposure to one dose versus two doses. Women were categorised as exposed regardless of the time between vaccination and birth, which ranged from one to 21 weeks. The numbers of pregnancies associated with each outcome were small.

Rottenstreich et al, 2021. Covid-19 vaccination during the third trimester of pregnancy: rate of vaccination and maternal and neonatal outcomes, a multicentre retrospective cohort study [24]

This retrospective cohort study aimed to compare composite adverse maternal outcomes and composite adverse neonatal outcomes between people vaccinated with Comirnaty in the third trimester and unvaccinated pregnant people. The study was conducted at two medical centres that account for 16% of deliveries in Israel between 19 January 2021 and 27 April 2021. People with current or previous COVID-19 disease were excluded.

The composite adverse maternal outcome included chorioamnionitis, postpartum haemorrhage, endometritis, blood transfusion, a caesarean delivery, ICU admission and a maternal hospital length of stay of longer than five days for vaginal delivery and longer than seven days for caesarean delivery. Some of these outcomes were also assessed individually. Secondary outcome analyses were only performed for people who received two doses of the vaccine.

The composite adverse neonatal outcome included intrauterine fetal death (IUFD), Apgar score of ≤7 at 1 minute, Apgar score of ≤7 at 5 minutes, admission to neonatal intensive care unit, neonatal asphyxia, intracranial haemorrhage, meconium aspiration syndrome, hyperbilirubinaemia, neonatal seizures, neonatal hypoglycaemia, neonatal sepsis and use of mechanical ventilation. These outcomes were also assessed individually.

There were 1,775 deliveries included in the study, of which 712 were in vaccinated people and 1,063 were in unvaccinated people. Those who had received two doses of the vaccine were older, and more likely to have had previous miscarriage, caesarean delivery or fertility treatment.

The proportion of deliveries affected by the composite adverse maternal outcome was not significantly different between vaccinated and unvaccinated people (24.2% vs 23.6%, p=0.79). In the multivariate analysis, the adjusted odds ratio for the composite maternal outcome was 0.8 (95% CI 0.61–1.03).

The proportion of deliveries affected by the composite adverse neonatal outcome was significantly lower in the vaccinated group compared with the unvaccinated group (7.9% vs 11.4%, p=0.02). The adjusted odds ratio for the composite neonatal outcome was 0.5 (95% CI 0.36–0.74).

The study did not find an association between COVID-19 vaccination during the third trimester and poorer maternal or neonatal outcomes. The authors note that people with asymptomatic previous or current SARS-CoV-2 infection may have been inadvertently included in the study. Information on the interval between vaccination and delivery was not available. The numbers of deliveries with rarer adverse outcomes were too small to detect any potential differences between the vaccinated and unvaccinated group.

Lipkind et al, 2022. Receipt of COVID-19 vaccine during pregnancy and preterm or small-for-gestational-age at birth — eight integrated health care organizations, United States, December 15, 2020-July 22, 2021 [25]

This report is an early release from the Centres for Disease Control and Prevention via the Morbidity and Mortality Weekly Report. This retrospective cohort study evaluates if there is an association between COVID-19 vaccination and preterm birth or small-for-gestational-age at birth, accounting for time-dependent vaccine exposures and propensity to be vaccinated. Pregnancies with estimated start or last menstrual period between 17 May 2020 and 24 October 2020 were eligible for inclusion and multiple gestation pregnancies were excluded. The data was obtained from the Vaccine Safety Datalink, which collects electronic health data from nine health care organisations representing three percent of the United States population.

There were 46,079 pregnant people with live births and gestational age available, of whom 10,064 received at least one dose of a COVID-19 vaccine. Nearly all (98.3%) of these people were vaccinated during the second or third trimester. There was no association between vaccination and preterm birth (adjusted hazard ratio [aHR] 0.91; 95% CI 0.82–1.01). There was also no association between vaccination and being small for gestational age at birth (aHR 0.95; 95% CI 0.87–1.03). There was also no increased risk when results were stratified by vaccine dose or trimester of vaccination (table 7).

Table 5: Preterm births, small-for-gestational-age births, and adjusted hazard ratios among women receiving COVID-19 vaccine during pregnancy compared with unvaccinated pregnant women — eight U.S. health care organizations,† December 15, 2020–July 22, 2021. Lipkind et al, 2022 [25]*

Event	No. of subjects	Prevalence (events per 100 live births)	aHR§ (95% CI)
Preterm birth¶			
Full population	**46,079**	**6.6**	**NA**
No COVID-19 vaccines during pregnancy	36,015	7.0	Ref
Any COVID-19 vaccine during pregnancy	10,064	4.9	0.91 (0.82–1.01)
mRNA vaccine, 1 dose	1,759	7.7	0.78 (0.66–0.93)
mRNA vaccine, 2 doses	7,881	4.3	0.97 (0.86–1.10)
Second trimester**	3,668	6.4	1.05 (0.90–1.23)
Third trimester**	6,224	4.0	0.82 (0.72–0.94)
Small-for-gestational-age at birth††			
Full population	**40,627**	**8.2**	**NA**
No COVID-19 vaccines during pregnancy	31,699	8.2	Ref
Any COVID-19 vaccine during pregnancy	8,928	8.2	0.95 (0.87–1.03)
mRNA vaccine, 1 dose	1,576	8.2	0.92 (0.80–1.07)
mRNA vaccine, 2 doses	6,982	8.3	0.98 (0.89–1.08)
Second trimester**	3,226	8.6	1.00 (0.86–1.17)
Third trimester**	5,561	8.0	0.93 (0.85–1.02)

Abbreviations: aHR = adjusted hazard ratio; NA = not applicable; Ref = referent group.
* Associations were estimated using a time-dependent covariate Cox model with inverse probability weighting and COVID-19 disease status as a time-dependent covariate.
† Kaiser Permanente: Colorado, Northern California, Northwest, Southern California, and Washington; Denver Health (Colorado); HealthPartners (Minnesota); and Marshfield Clinic (Wisconsin).
§ Inverse probability weighting was computed using a generalized additive model for receiving 1 or 2 doses of COVID-19 vaccines during pregnancy with calendar week of pregnancy start date, maternal age, race/ethnicity, prenatal care adequacy, maternal comorbidities, state level COVID-19 average test positivity during the second trimester, neighborhood poverty, and Vaccine Safety Datalink site as covariates.
¶ <37 weeks' gestational age.
** Based on timing for first or only vaccine dose; first trimester vaccinations are not included in analyses stratified by trimester because few exposures occurred (172).
†† Birthweight for gestational age <10th percentile.

The authors identified that some vaccinations may have been missed, causing possible bias towards the null. There was also missing information on confounders such as previous SGA or preterm birth and previous SARS-CoV-2 infection. The decreased risks of preterm birth with third trimester vaccination and receipt of only one dose were thought to be due to residual immortal time bias.

Goldshtein et al, 2022. Association of BNT162b2 COVID-19 vaccination during pregnancy with neonatal and early infant outcomes [26]

This cohort study aimed to examine whether vaccination with Comirnaty during pregnancy is associated with adverse neonatal and early infant outcomes. Data were extracted from a public health fund database that represents 26.7% of the population of Israel. Records with missing maternal linkage or important covariate data were excluded. The study included all singleton births between 1 March 2021 and 31 September 2021. The primary outcomes were small birth weight for gestational age (SGA) and preterm birth. Exploratory outcomes included inpatient hospitalisations, recorded congenital anomalies, jaundice requiring phototherapy, and all-cause death over the study period.

After exclusions, 24,288 eligible newborns were identified, of whom 16,697 were born to mothers vaccinated during pregnancy. The vaccinated group had older maternal age at birth, higher influenza vaccine uptake, lower likelihood of belonging to an ethnic minority and greater likelihood of living in more affluent areas.

The study found no association between vaccination and SGA (RR = 0.97; 95% CI, 0.87-1.08) or overall preterm birth (RR = 0.95; 95% CI, 0.83-1.10) (table 8). An analysis of first trimester vaccination showed

similar results and also found no adverse association with congenital abnormalities (table 9). No association was found for the exploratory outcomes of hospitalisations and infant death. An association was found between vaccination and jaundice requiring phototherapy in the first trimester analysis and in the sensitivity analysis where mothers with prior SARS-CoV-2 infection were excluded. The authors attributed this to possible confounding from a higher rate of smoking in the vaccinated group. The numbers of these rarer outcomes are too small to draw definitive conclusions.

Table 6: Early neonatal and infant outcomes. Goldshtein et al, 2022 [26]

	Pre-IPTW			Post-IPTW[a]		
	Unvaccinated (n = 7591)	Vaccinated (n = 16 697)	Risk ratio (95% CI)	Unvaccinated (n = 7452)	Vaccinated (n = 16 738)	Risk ratio (95% CI)
Follow-up time, d	152 (88-209)	126 (76-179)		130 (71-197)	134 (81-185)	
Gestational age at delivery, No.(%)						
<37 wk (Overall preterm)	315 (4.1)	730 (4.4)	1.10 (0.95-1.27)	358 (4.8)	699 (4.2)	0.95 (0.83-1.10)
<32 wk (Early preterm)	48 (0.6)	60 (0.4)	0.52 (0.33-0.82)	62 (0.8)	60 (0.4)	0.45 (0.29-0.70)
32-36 wk (Late preterm)	267 (3.5)	670 (4.0)	1.18 (1.02-1.38)	296 (4.0)	638 (3.8)	1.03 (0.89-1.20)
Birth weight, No. (%)						
SGA	468 (6.7)	1040 (6.6)	0.98 (0.88-1.09)	473 (6.9)	1053 (6.7)	0.97 (0.87-1.08)
Low birth weight, <2500 g	324 (4.6)	730 (4.6)	0.98 (0.86-1.13)	352 (5.1)	705 (4.5)	0.89 (0.78-1.01)
Very low birth weight, <1500 g	43 (0.6)	47 (0.3)	0.44 (0.27-0.70)	53 (0.8)	49 (0.3)	0.41 (0.26-0.65)
Unknown, No.	619	833		561	932	
All-cause hospitalizations, No. (%)						
Neonatal (1-28 d after birth)	416 (5.5)	916 (5.5)	1.00 (0.89-1.13)	408 (5.5)	911 (5.4)	0.99 (0.88-1.12)
Postneonatal (>28 d after birth)	475 (6.3)	777 (4.7)	0.87 (0.78-0.98)	398 (5.3)	846 (5.1)	0.95 (0.84-1.07)
Phototherapy	71 (0.9)	205 (1.2)	1.31 (1.01-1.73)	73 (1.0)	203 (1.2)	1.24 (0.95-1.63)
Infant death over the study period	8 (0.1)	22 (0.1)	1.43 (0.66-3.43)	13 (0.2)	24 (0.1)	0.84 (0.43-1.72)

Abbreviations: IPTW, inverse probability of treatment weights; SGA, small for gestational age.

[a] IPTW was used to balance groups in terms of maternal age, conception timing, parity, seasonal influenza vaccination, population subgroup, and socioeconomic status. Post-IPTW numbers slightly differ from crude pre-IPTW because of propensity weighting.

Table 7: Neonatal and early infant outcomes for first trimester vaccination. Goldshtein et al, 2022 [26]

	Pre IPTW			Post IPTW[b]		
	Unvaccinated (n = 3584)	Vaccinated (n = 2134)	Risk ratio (95% CI)	Unvaccinated (n = 3570)	Vaccinated (n = 2032)	Risk ratio (95% CI)
Follow-up time, d	86 (57-116)	55 (42-71)		73 (48-105)	63 (48-83)	
Gestational age at delivery, No. (%)						
<37 wk (Overall preterm)	218 (6.1)	158 (7.9)	1.15 (0.91-1.46)	236 (6.6)	126 (6.2)	0.87 (0.67-1.12)
<32 wk (Early preterm)	40 (1.1)	19 (0.9)	0.39 (0.15-0.88)	47 (1.3)	16 (0.8)	0.24 (0.07-0.61)
32-36 wk (Late preterm)	178 (5.0)	149 (7.0)	1.30 (1.01-1.67)	189 (5.3)	110 (5.4)	1.00 (0.76-1.30)
Birth weight, No. (%)						
SGA (small for gestational age)	223 (6.8)	150 (7.5)	1.10 (0.89-1.36)	226 (6.9)	145 (7.9)	1.14 (0.92-1.40)
Low birth weight, <2500 g	188 (5.8)	153 (7.6)	1.12 (0.88-1.43)	206 (6.3)	125 (6.8)	0.95 (0.74-1.22)
Very low birth weight, <1500 g	33 (1.0)	16 (0.8)	0.41 (0.15-0.93)	40 (1.2)	12 (0.6)	0.23 (0.07-0.61)
Unknown, No.	327	124		314	198	
Congenital anomalies, No. (%)						
Heart malformations	49 (1.4)	27 (1.3)	0.93 (0.57-1.47)	44 (1.2)	19 (0.9)	0.75 (0.43-1.26)
Major heart malformations[c]	51 (1.4)	16 (0.7)	0.53 (0.29-0.90)	49 (1.4)	13 (0.6)	0.46 (0.24-0.82)
Any congenital anomalies	87 (2.4)	43 (2.0)	0.83 (0.57-1.19)	76 (2.1)	30 (1.5)	0.69 (0.44-1.04)
All-cause hospitalizations						
Neonatal (1-28 d after birth)	210 (5.9)	115 (5.4)	0.92 (0.73-1.15)	201 (5.6)	99 (4.9)	0.86 (0.67-1.09)
Postneonatal (>28 d after birth)	151 (4.2)	34 (1.6)	0.72 (0.49-1.03)	121 (3.4)	43 (2.1)	0.78 (0.54-1.09)
Phototherapy	33 (0.9)	42 (2.0)	2.14 (1.36-3.40)	36 (1.0)	34 (1.7)	1.71 (1.06-2.73)
Infant death over the study period	6 (0.2)	4 (0.2)	1.68 (0.43-5.88)	8 (0.2)	3 (0.1)	0.69 (0.14-2.41)

Abbreviations: IPTW, inverse probability of treatment weights; SGA, small for gestational age.

[a] This subgroup analysis included gestations exposed in the first trimester and unexposed during pregnancy with conception timing within the range of the exposed group conception (September 2020 and later).

[b] IPTW was used to balance groups in terms of maternal age, conception timing, parity, seasonal influenza vaccination, population subgroup, and socioeconomic status. Post-IPTW numbers slightly differ from crude pre-IPTW because of propensity weighting.

[c] Major heart malformations were congenital heart malformations other than ventricular septal defect and patent foramen ovale.

This study is underpowered to detect potential differences in rarer outcomes following first trimester vaccination and accumulation of further follow-up time is needed. Another limitation is that the study population is limited to newborns registered in the database and may not capture all cases of very early infant mortality.

Literature on general safety profile in pregnant people

Sadarangani et al, 2022. Safety of COVID-19 vaccines in pregnancy: a Canadian National Vaccine Safety (CANVAS) Network study (preprint) [27]

This pre-print study aimed to determine significant health events amongst pregnant females after COVID-19 vaccination, compared with unvaccinated pregnant controls and vaccinated non-pregnant individuals. Participants were actively recruited and asked to complete surveys via email on any AEFIs during the seven days following each vaccine dose, or in the prior seven days in the case of unvaccinated participants. The study included females reporting pregnancy and non-pregnant females from the age groups.

The primary endpoint was 'significant health event', defined as a new or worsening health event that caused absence from work or school, medical consultation or prevented normal activities. 'Serious health event' was a secondary endpoint, defined as any event resulting in emergency department visit or hospitalisation. All events were self-reported and not medically confirmed.

Of the mRNA-vaccinated pregnant individuals, 4.0% (226) and 7.3% (227) reported a significant health event after dose one and dose two, respectively. The most frequently reported events were malaise, myalgia, headache and respiratory tract infection. By comparison, 3.2% (11) pregnant unvaccinated participants reported a significant health event. Serious health events were reported by 0.6%-0.9% of pregnant participants, depending on vaccine type. Miscarriage/stillbirth was reported at similar rates between unvaccinated and vaccinated participants after dose one (n=7 [2.1%] and n=83 [1.5%], respectively).

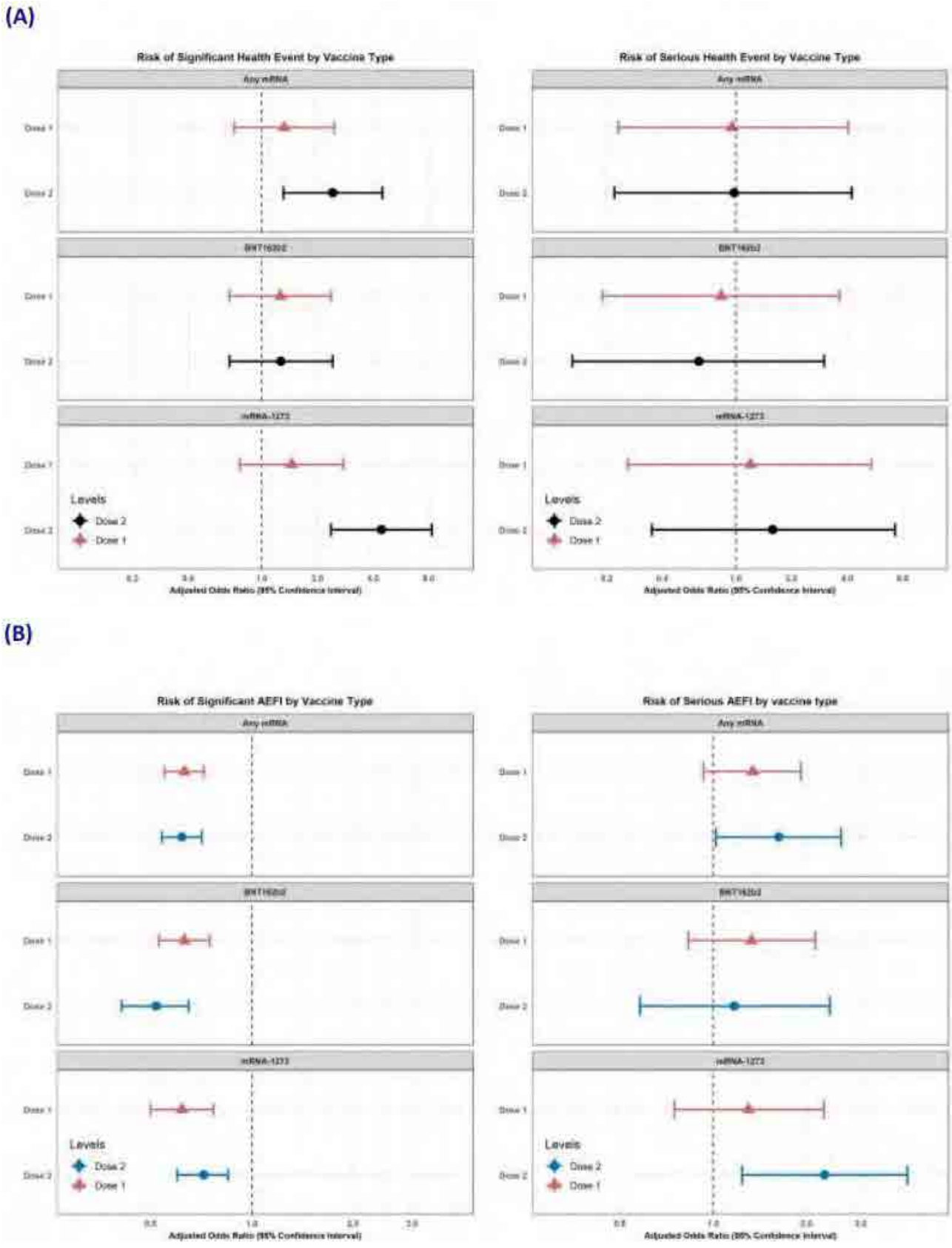
In the multivariate analysis that adjusted for age group, prior COVID-19 infection and trimester (figure 8), there was an increased risk of a significant health event within seven days of dose two of any mRNA vaccine (aOR: 2.4; 95% CI: 1.3-4.5) or dose two of Spikevax (aOR: 4.4, 95% CI: 2.4-8.3) for pregnant vaccinated individuals, compared with pregnant unvaccinated controls. These associations disappeared in the sensitivity analyses that were restricted to participants reporting good health status and events requiring medical care. There was no association between vaccination and serious health events.

When comparing vaccinated pregnant and vaccinated non-pregnant people, significant AEFI rates (excluding injection site reactions) were consistently lower among pregnant people across all mRNA vaccine types and doses. Overall, 4.0% and 7.3% of pregnant people reported a significant AEFI after dose one and dose two, respectively, compared with 6.3% and 11.3% for non-pregnant people.

In the multivariate analysis (figure 8), pregnancy was associated with a decreased risk of significant health events for any mRNA vaccine or dose. There was no association between pregnancy status and significant health events when the analysis was restricted to events requiring medical care. For the secondary endpoint of serious events, dose two of Spikevax was associated with a higher risk in pregnant participants compared with non-pregnant participants (aOR 2.3; 95% CI: 1.2-4.2). It should be noted that this result is based on very small numbers of serious events in pregnant people (11).

Limitations of this study include the potential for recall bias, lack of medical confirmation of serious events and relatively small sample size.

Figure 8: Multivariable logistic regression analyses comparing significant and serious health events amongst (A) pregnant people, comparing vaccinated with unvaccinated individuals and (B) vaccinated people, comparing pregnant with non-pregnant individuals. Sadarangani et al, 2022. [27]



Nakahara et al, 2022. Safety-related outcomes of novel mRNA COVID-19 vaccines in pregnancy [28]

This cohort study examined the safety profile of mRNA COVID-19 vaccination in 83 pregnant people and 166 age-matched controls vaccinated between December 2020 and January 2021. The primary outcome was frequency of any vaccine-related complaint and secondary outcomes included specific complaints and positive COVID-19 test.

The frequency of complaints following vaccination was not different between pregnant and non-pregnant patients (18.1 vs. 16.9%, p = 0.201). Pregnant patients were more likely to report fever (4.8 vs. 0.6%, p = 0.044) and gastrointestinal symptoms (4.8 vs. 0%, p = 0.012).

Literature on fertility

Aharon et al, 2022. In vitro fertilization and early pregnancy outcomes after Coronavirus Disease 2019 (COVID-19) vaccination [29]

This retrospective cohort study examined whether COVID-19 vaccination was associated with differences in fertilisation rate in people who underwent controlled ovarian hyperstimulation (COH) or single euploid frozen-thawed embryo transfer (FET) at a single academic centre. Secondary outcomes for COH included eggs retrieved, mature oocytes retrieved, mature oocytes ratio, blastulation rate, and euploid rate. Secondary outcomes for FET included pregnancy rate, ongoing pregnancy rate, biochemical pregnancy loss rate, and clinical pregnancy loss rate.

The exposed group consisted of patients who had received two doses of either Comirnaty or Spikevax at least 14 days before starting medication for their procedure and the control group consisted of unvaccinated patients. The first cycle for each patient between February and September 2021 was included.

The COH group included 222 fully vaccinated patients and 983 unvaccinated patients. The adjusted analysis found no association between vaccination and fertilisation rate ($\beta = 0.02 \pm 0.02$, $P = 0.20$) or any of the secondary outcomes.

The FET group included 214 vaccinated patients and 733 unvaccinated patients. The adjusted analysis found no association between vaccination and fertilisation rate (aOR = 0.79, 95% CI 0.54–1.16) or any of the secondary outcomes.

One strength of this study is that it captures early implantation and early pregnancy losses that may be unrecognised in other studies. These findings provide further reassurance that COVID-19 vaccination is not associated with impaired fertility or early pregnancy losses. Limitations include unknown SARS-CoV-2 infection status of the participants and small number of vaccinated participants. Fetal and birth outcomes were not assessed in this study.

Hillson et al, 2021. Fertility rates and birth outcomes after ChAdOx1 nCoV-19 (AZD1222) vaccination [30]

This correspondence published in the Lancet analyses the pregnancies that have occurred in four ongoing clinical trials for Vaxzevria. Pregnant people were excluded from the trials, but any pregnancies occurring after vaccination are followed up until three months after birth.

The fertility outcome analysis set included 93 pregnant women (50 vaccinated and 43 control). There was no significant difference in fertility of vaccinated and unvaccinated participants as measured by the total number of pregnancies or by viable pregnancies (table 11).

Table 8: Fertility rates. Hillson et al, 2021 [30]

	ChAdOx1 nCoV-19 (n=4925)	Control (n=4830)*	Fertility rate ratio (95% CI)	p value
Pregnant women (fertility rate)†	50 (0·0102)	43 (0·0089)	1·14 (0·76–1·71)	0·53
Viable pregnancies (fertility rate)‡	32 (0·0065)	29 (0·0060)	1·08 (0·66–1·79)	0·80

Data are n (fertility rate) unless otherwise stated. *11 women vaccinated during pregnancy were included in the controls (eight received AZD1222 and three mRNA vaccines). †28 pregnant women (six in the control vaccine group and 22 in the AZD1222 group) were excluded from this fertility analysis because they were unmasked to vaccine allocation before becoming pregnant. ‡Viable pregnancies did not include pregnant women who had a termination or miscarriage.

Table 1: Fertility rates

The pregnancy outcome analysis set included 107 women (72 vaccinated and 35 control). Controls who were subsequently vaccinated were excluded from the analysis. There were no differences in the pregnancy outcomes of miscarriage or termination, or preterm birth (table 12). Analyses that exclude Brazilian data were conducted as pregnancy termination is illegal in Brazil. Most pregnancies were still ongoing at the time of analysis. There were no stillbirths or neonatal deaths; however, this paper defines miscarriage as pregnancy loss before 23 weeks gestation while the New Zealand definition is before 20 weeks.

Table 9: Pregnancy outcomes. Hillson et al, 2021 [30]

	ChAdOx1 nCoV-19 (n=72)	Control (n=35)	Risk ratio (95% CI)	p value
Miscarriage, excluding Brazilian data	6/43 (14%)	5/24 (21%)	0·67 (0·23–1·97)	0·51
Termination, excluding Brazilian data	8/43 (19%)	6/24 (25%)	0·74 (0·29–1·89	0·55
Miscarriage or termination, all	23/72 (32%)	13/35 (37%)	0·86 (0·50–1·49)	0·67
Preterm birth	3/10 (30%)	0/5 (0%)	Not calculable	0·51*
Full-term birth	7/72 (10%)	5/35 (14%)	0·68 (0·23–1·99)	0·52
Ongoing pregnancy	39/72 (54%)	17/35 (49%)	1·12 (0·75–1·67)	0·68

Data are n/N (%) unless otherwise stated. *Two-sided p value.

Table 2: Pregnancy outcomes

Periodic Benefit Risk Evaluation Reports (PBRERs)

s 9(2)(ba)(ii)

[redacted]

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[redacted]

EXPERT ADVICE

This memo will be presented to the COVID-19 Vaccine Independent Safety Monitoring Board (CV-ISMB).

CONCLUSION AND PROPOSED ACTIONS

Pregnancy is associated with increased risk of severe COVID-19 disease and death. The risk of hospital admissions has been found to be three times higher and the rate of ICU care five times higher than in non-pregnant women. Obesity, hypertension, asthma, autoimmune disease, diabetes and older age are also risk factors for severe COVID-19 disease during pregnancy. Infants of infected mothers have increased risks of preterm delivery and neonatal ICU admission [1].

As of 22 March 2022, of a total of 60,378 cases, there were 462 AEFI case reports in females aged 15-49 years where pregnancy was indicated using the checkbox on the reporting form. All reports were for Comirnaty apart from one report for Vaxzevria. The reporting patterns were similar to that of the general population. The most frequently reported events were those expected after vaccination, such as headache, dizziness, injection site pain, nausea and lethargy.

As of 22 March 2022, there were 66 reports of spontaneous abortion, abortion or missed abortion and two reports of stillbirth. Of the 66 cases reporting spontaneous abortion, abortion or missed abortion, 49 occurred in the first trimester, 5 occurred in the second trimester and 12 occurred at during early pregnancy or unknown gestation. Spontaneous abortion is common, occurring in around 1 in 5 clinically recognised pregnancies. The reports received do not highlight any safety concerns, although they contain limited information.

Scientific literature supporting the safety of COVID-19 vaccination in pregnancy has accumulated since the previous memo dated 22 October 2022. The studies published to date have not found an increased risk of a range of maternal or neonatal adverse pregnancy outcomes, including preterm birth, small for gestational age at birth and spontaneous abortion [22-26]. No adverse effects on fertility have been detected [29, 30].

There are no safety concerns in general with the use of non-live vaccines in pregnancy. The New Zealand spontaneous reporting data and scientific literature overwhelmingly support the safety COVID-19 vaccination in pregnancy. Routine pharmacovigilance activities should continue.

RECOMMENDATIONS

It is recommended that:

1.	Routine pharmacovigilance activities are continued	Yes/No

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Document 13

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28 February 2022

To whom it may concern,

The COVID-19 Vaccine Independent Safety Monitoring Board (CV-ISMB) works alongside the Centre for Adverse Reactions Monitoring (CARM) to assist with pharmacovigilance monitoring of COVID-19 vaccines. The CV-ISMB is a panel of experts from clinical medicine, biostatistics, public health, immunology, and microbiology that informs and supports CARM during assessments into the strength of association between COVID-19 vaccination and an adverse event following immunisation (AEFI).

The CV-ISMB is aware that the parameters and processes for coronial referral are well established and, therefore, would like to remind and encourage clinicians to continue to refer sudden deaths with a temporal association to COVID-19 vaccination for coronial investigation. The CV-ISMB maintains that the clinicians involved in the care of the patient are best placed to decide on the instances where this may be necessary.

The CV-ISMB considers that a coronial investigation may help the family understand what happened and will support the pharmacovigilance of the COVID-19 vaccine in New Zealand.

Please note that the role of CARM and the CV-ISMB is to consider the strength of association between vaccination and the reported medical events. An investigation into the cause of death is under the authority of the Office of the Chief Coroner.

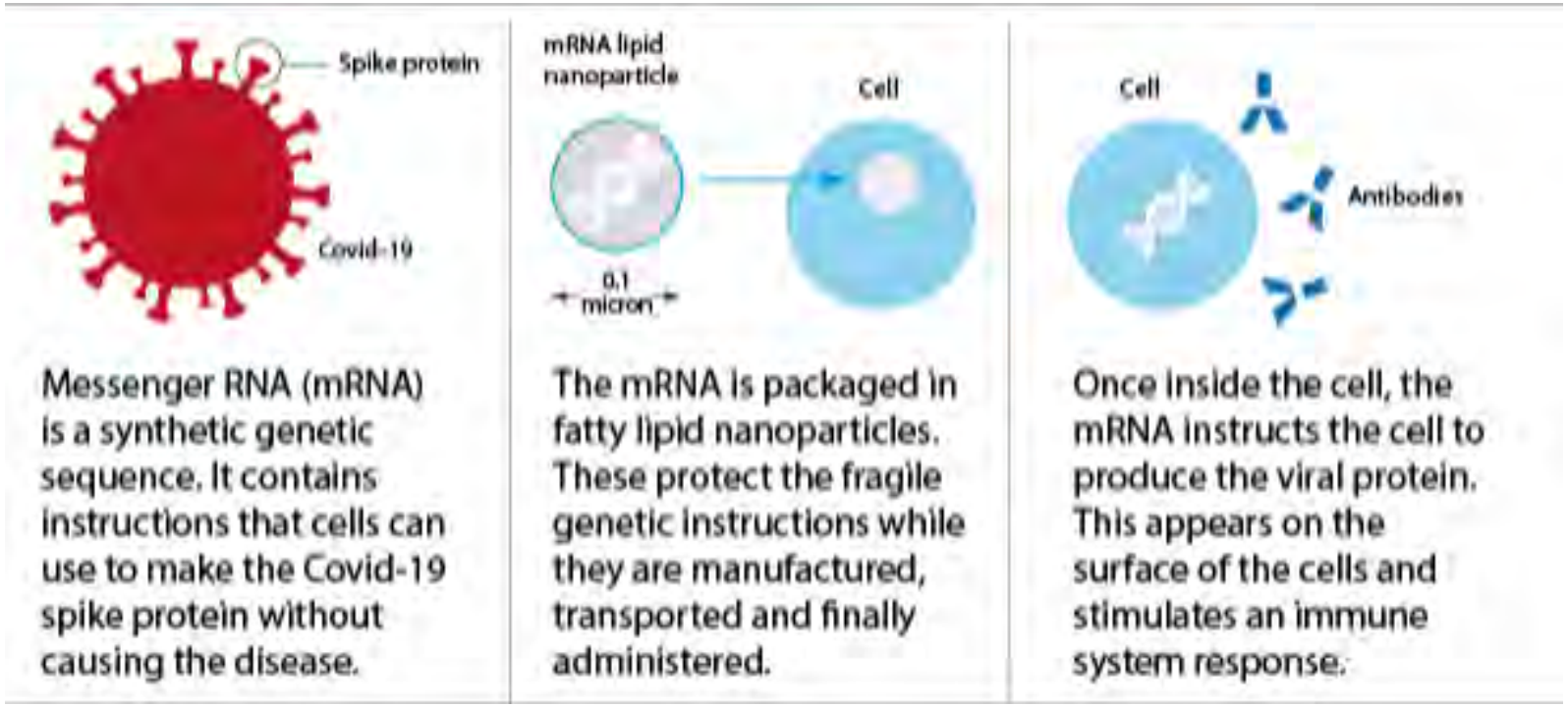
Yours faithfully,

Dr Tim Hanlon
Group Manager Post Event
National Immunisation Programme

Document 14

Comirnaty and mechanisms for adverse reactions

How mRNA vaccines work:



The platform for mRNA vaccines are nucleoside modified mRNA.

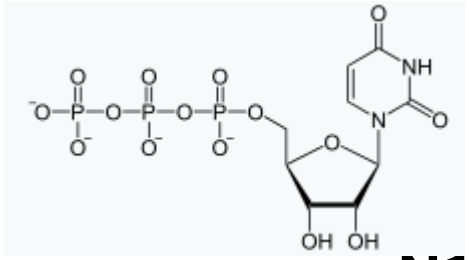
Innate immune system and mRNA vaccine

- The innate immune system is the first line of defense against invading pathogens.
- Selected DNA and RNA molecules (that mimic pathogens) have the unique property to activate the immune system.
- RNA signals through human TLR3, TLR7, and TLR8 but nucleoside modification can take away this activity.
- Nucleoside modifications also suppress the potential of RNA to activate DCs.

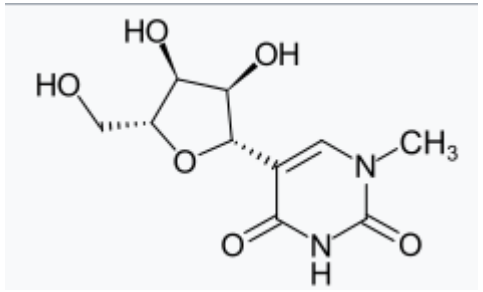
Kariko et al. 2005, 2008, 2011

Comirnaty mRNA modifications

- Nucleoside modification:



uridine (UTP) residues replaced by



N1-methyl-3’ -pseudouridine ($^{m1}\Psi$TP) modifications

to enhance translation of the in vitro transcribed mRNA sequences by reducing its innate immunogenicity. Has been shown to significantly decrease expression of cytokines and activation markers, such as TNF-α, interferon and IL-12.

- mRNA is encapsulated in lipid nanoparticles to enhance uptake by the host cells.

- Note that Moderna vaccine has 3x mRNA concentration (100vs 30 µg) compared to Comirnaty

Document 14

Genetic predisposition?

Bozkurt et al 2021:

- In **certain individuals** with **genetic predisposition**, the immune response to mRNA may **not** be turned down and may **drive the activation** of an **aberrant** innate and acquired immune response.
- The dendritic cells or Toll-like receptor expressing cells exposed to RNA may **still have the capacity** to express cytokines and activation markers.
- The immune system may therefore detect the **mRNA in the vaccine as an antigen**, resulting in activation of proinflammatory cascades and immunologic pathways.

May play a role in the development of myocarditis as part of a systemic reaction in certain individuals.

Other mechanisms ?

- Molecular mimicry between the spike protein and self-antigens - time frame and dose 1 reaction do not support that
- A delayed hypersensitivity reaction, such as serum sickness–like reaction or eosinophilic myocarditis – not supported by current data according to Bozkurt.
- Leakage of mRNA into blood – myocarditis induced in mice by iv not im administration (Li et al 2021)
- Reactions after dose 1: robust inflammation induced by the LNPs. Reactions after dose 2: similar but more robust inflammatory reaction + adaptive immune response formed after dose 1 - from mice studies (Ndeupen et al 2021).
- The SARS-CoV-2 spike glycoprotein attaches to endothelium via ACE enzyme 2 which results in complement-mediated microvascular injury where endothelia have high ACE2+ expression. The myocardium is one such place - seen in skin reactions (Magro et al 2021).
- Sex differences: The prevalence of myocarditis in young males may reflect signal potentiation by male hormones, cardio protection by female hormones or other hormone independent differences.