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3 May 2023

J Bruning

By email: fyi-request-22343-3dbaa817@requests.fyi.org.nz  
Ref: H2023022968

Tēnā koe

### **Response to your request for official information**

Thank you for your request under the Official Information Act 1982 (the Act) to Manatū Hauora (the Ministry of Health) on 31 March 2023 for information regarding COVID-19 and pregnancy. You requested:

*Q(1) Please provide the dates and titles of all risk/benefit analyses undertaken which reviewed the data/science of risks and benefits to the pregnant mother and fetus for the primary course of injection of Comirnaty BNT162b2. This includes for those who have immunocompromised conditions and healthy women.*

I have identified 2 memoranda in scope of this part of your request. These are reviews presented to the COVID-19 Vaccine Independent Safety Monitoring Board (CV-ISMB) regarding the safety of Comirnaty in pregnancy. These are itemised in Appendix 1 of this letter and copies of the documents are enclosed. Where information is withheld, this is noted in the document itself. I have considered the countervailing public interest in release in making this decision and consider that it does not outweigh the need to withhold at this time.

*On 3 November 2021 the Memo 'Temporary Medical Exemptions for the COVID-19 Vaccine: COVID-19 Vaccine Technical Advisory Group (CV TAG) recommendations' stated 'Pregnancy is not a valid reason for exemption in the absence of any of the criteria listed in the above table. Pregnancy is associated with higher risk from COVID-19 compared to the general population and therefore this group are a priority for vaccination.'*

*Q(2) As it is well known that doctors are extremely precautionous and often refrain from prescribing drugs without a long safety profile, please can you provide:  
(a) The latest reviews/reports/advice justifying and specifically applied as rationale for the above statement that pregnancy is higher risk, as at November 2021.*

*In February 2022, the CV TAG recommended that 'A booster dose of the COVID-19 vaccine should be given from 3 months after the primary course to all eligible people aged 18 years and over, including immunocompromised individuals and pregnant persons.'*

*(b) The scientific literature provided to doctors between October 2021- February 2022 justifying this recommendation.*

Please refer to the following COVID-19 Vaccine Technical Advisory Group (CV TAG) memos for all reports and data used to inform the decision available on the Manatū Hauora website here: [www.health.govt.nz/about-ministry/leadership-ministry/expert-groups/covid-19-vaccine-technical-advisory-group-cv-tag](http://www.health.govt.nz/about-ministry/leadership-ministry/expert-groups/covid-19-vaccine-technical-advisory-group-cv-tag).

These are provided as the relevant CV TAG memos up to and including, November 2021:

- [www.health.govt.nz/system/files/documents/pages/20210527 - cv tag recommendations for pfizer covid-19 vaccine in pregnancy.pdf](http://www.health.govt.nz/system/files/documents/pages/20210527_-_cv_tag_recommendations_for_pfizer_covid-19_vaccine_in_pregnancy.pdf).
- [www.health.govt.nz/system/files/documents/pages/20211103 - cv tag - medical exemption.pdf](http://www.health.govt.nz/system/files/documents/pages/20211103_-_cv_tag_-_medical_exemption.pdf).

These are provided as the relevant CV TAG memos up to and including, February 2022.

- [www.health.govt.nz/system/files/documents/pages/20211217 - cv-tag - booster vaccinations update.pdf](http://www.health.govt.nz/system/files/documents/pages/20211217_-_cv-tag_-_booster_vaccinations_update.pdf).
- Temporary Medical Exemptions for the COVID-19 Vaccine: COVID-19 Vaccine Technical Advisory Group (CV TAG) recommendations: [www.health.govt.nz/system/files/documents/pages/20220125 - cv tag - booster vaccinations for pregnant people and immunocompromised.pdf](http://www.health.govt.nz/system/files/documents/pages/20220125_-_cv_tag_-_booster_vaccinations_for_pregnant_people_and_immunocompromised.pdf).
- [www.health.govt.nz/system/files/documents/pages/20220201 - cv tag recommendations on booster interval.pdf](http://www.health.govt.nz/system/files/documents/pages/20220201_-_cv_tag_recommendations_on_booster_interval.pdf).

*Q(3) Please provide the CV-TAG reviews/reports/advice which considered the risk benefit of booster doses of Comirnaty BNT162b2 to pregnant women, including for those with immunocompromised conditions and healthy women.*

Please see the following CV TAG memos for all reports and data used to inform the decision:

- [www.health.govt.nz/system/files/documents/pages/20220201 - cv tag recommendations on booster interval.pdf](http://www.health.govt.nz/system/files/documents/pages/20220201_-_cv_tag_recommendations_on_booster_interval.pdf)
- Update to recommendations on COVID-19 booster vaccinations for pregnant people and immunocompromised: COVID-19 Vaccine Technical Advisory Group (CV TAG) recommendations: [www.health.govt.nz/system/files/documents/pages/20220125 - cv tag - booster vaccinations for pregnant people and immunocompromised.pdf](http://www.health.govt.nz/system/files/documents/pages/20220125_-_cv_tag_-_booster_vaccinations_for_pregnant_people_and_immunocompromised.pdf)

I trust this information fulfils your request. Under section 28(3) of the Act, you have the right to ask the Ombudsman to review any decisions made under this request. The Ombudsman may be contacted by email at: [info@ombudsman.parliament.nz](mailto:info@ombudsman.parliament.nz) or by calling 0800 802 602.

Please note that this response, with your personal details removed, may be published on the Manatū Hauora website at: [www.health.govt.nz/about-ministry/information-releases/responses-official-information-act-requests](http://www.health.govt.nz/about-ministry/information-releases/responses-official-information-act-requests).

Nāku noa, nā



Jan Torres  
**Manager OIA Services**  
**Government and Executive Services**

## Appendix 1: List of documents for release

#	Date	Document details	Decision on release
1	23 March 2022	Memo: The Safety of COVID-19 vaccination during pregnancy 28963	<p>Some information withheld under the following sections of the Act:</p> <ul style="list-style-type: none"> <li>• 9(2)(g)(ii) to maintain the effective conduct of public affairs through the protection of such Ministers, members of organisations, officers, and employees from improper pressure or harassment</li> <li>• 9(2)(a) of the Act, to protect the privacy of natural persons.</li> <li>• section 9(2)(ba)(i) to protect information that is subject to an obligation of confidence and making it available would likely prejudice the supply of similar information, or information from the same source.</li> </ul>
2	22 October 2022	Memo: Pregnancy-related AEFI reports in New Zealand following administration of Comirnaty	<p>Some information withheld under the following sections of the Act:</p> <ul style="list-style-type: none"> <li>• 9(2)(g)(ii); and</li> <li>• 9(2)(a),</li> </ul>

# Memo

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

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## 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].

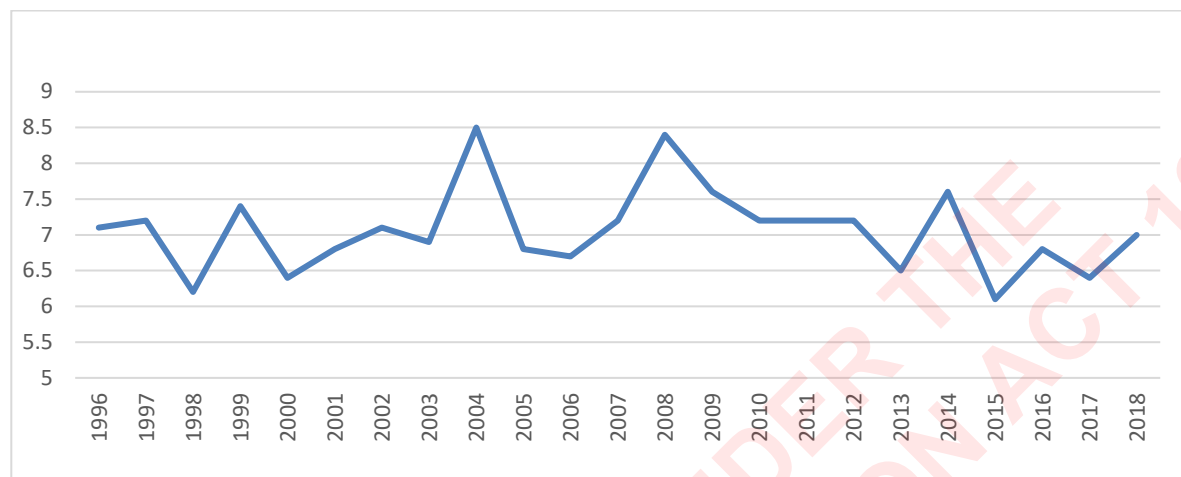
Chromosomal abnormalities, maternal anatomic abnormalities and significant trauma may also cause pregnancy loss. There can be multiple factors involved in second trimester pregnancy loss and often no cause is identified [4].

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  $\geq 400$  g birthweight or who were  $\geq 20$  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

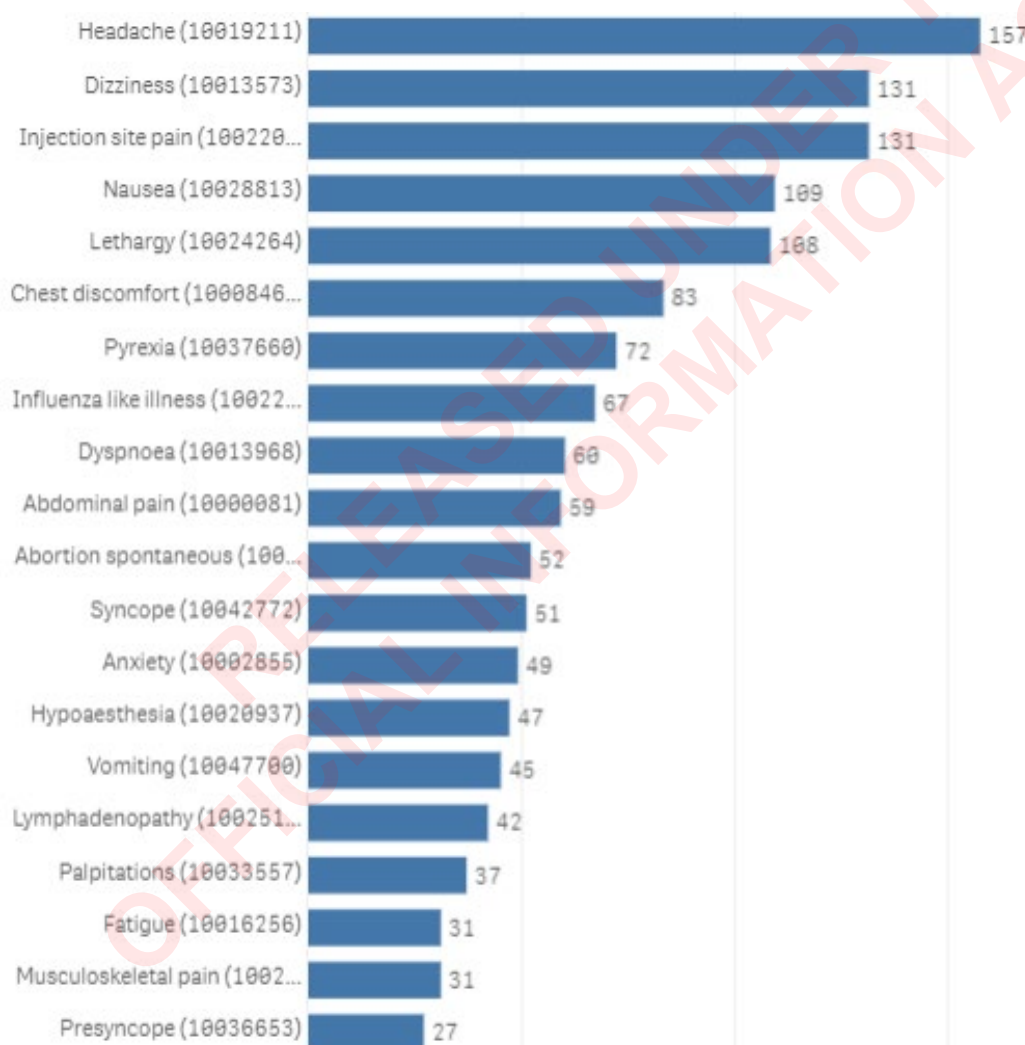
aged 16-49 years, which are also frequently reported in the overall population, with the exception of spontaneous abortion.

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

<b>AEFI term</b>	<b>Percentage of pregnant cases reporting AEFI</b>	<b>Percentage of all cases reporting AEFI</b>
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

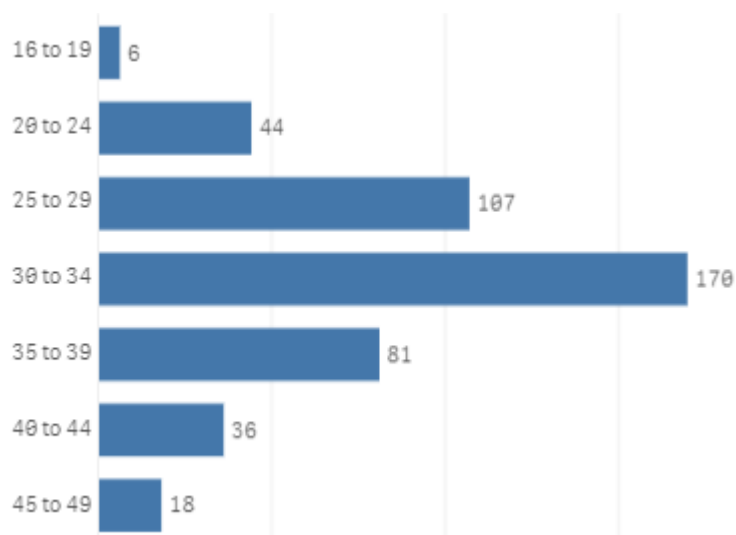
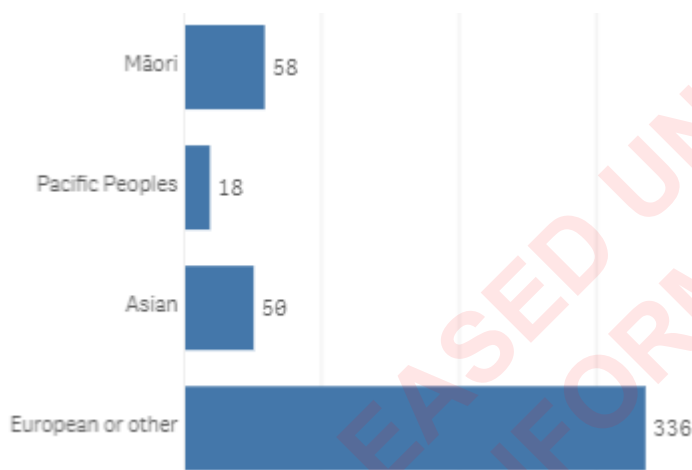


Figure 4: Ethnicity of pregnant cases



#### 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).

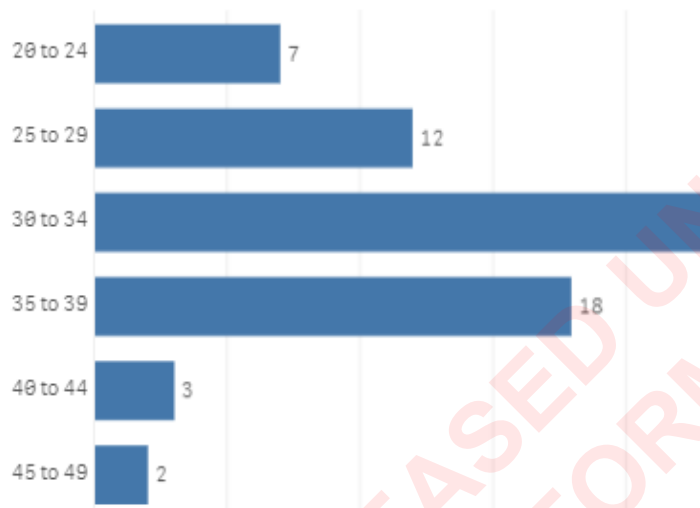
It should be noted that these terms include those selected by the reporter and may not be medically confirmed.

*Cases reporting pregnancy loss*

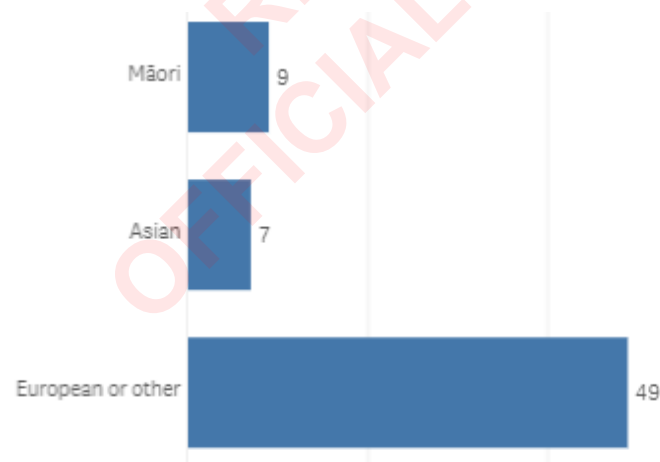
As of 22 March 2022, there were 66 reports coded with the terms spontaneous abortion, abortion or missed abortion and two cases coded with stillbirth. There are also three reports of fetal hypokinesia and one report of congenital abnormality, which was included in the October 2021 memo. The details of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

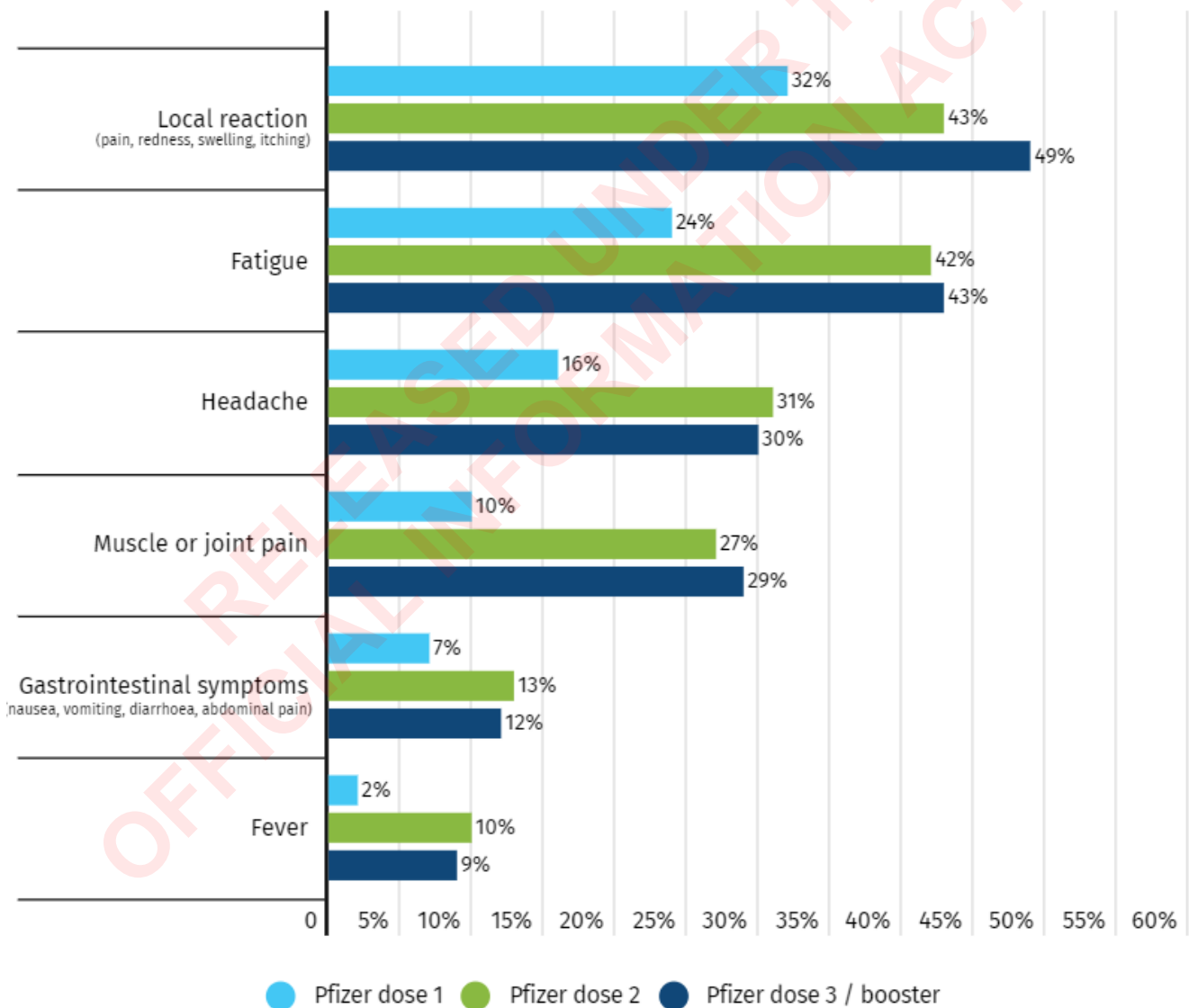


**Solicited reporting in Australia**

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]*

<b>Outcomes</b>	<b>Adjusted Odds ratio* (vaccinated vs. unvaccinated); 95% CI</b>
<b>Pregnancy complications diagnosed in late pregnancy</b>	
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
<b>Delivery and post-partum characteristics</b>	
Gestational age at delivery	$\beta = -0.07$ ; (-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
<b>Newborn characteristics</b>	
Birthweight, gr. (mean $\pm$ SD)	$\beta = -9.14$ ; (-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  $\leq 7$  at 1 minute, Apgar score of  $\leq 7$  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 <sup>§</sup> (95% CI)
<b>Preterm birth<sup>¶</sup></b>			
<b>Full population</b>	<b>46,079</b>	<b>6.6</b>	<b>NA</b>
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)
<b>Small-for-gestational-age at birth<sup>††</sup></b>			
<b>Full population</b>	<b>40,627</b>	<b>8.2</b>	<b>NA</b>
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.

*Goldshstein 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 <sup>a</sup>		
	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.

<sup>a</sup> 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 <sup>b</sup>		
	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 <sup>c</sup>	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.

<sup>a</sup> 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).

<sup>b</sup> 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.

<sup>c</sup> 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.

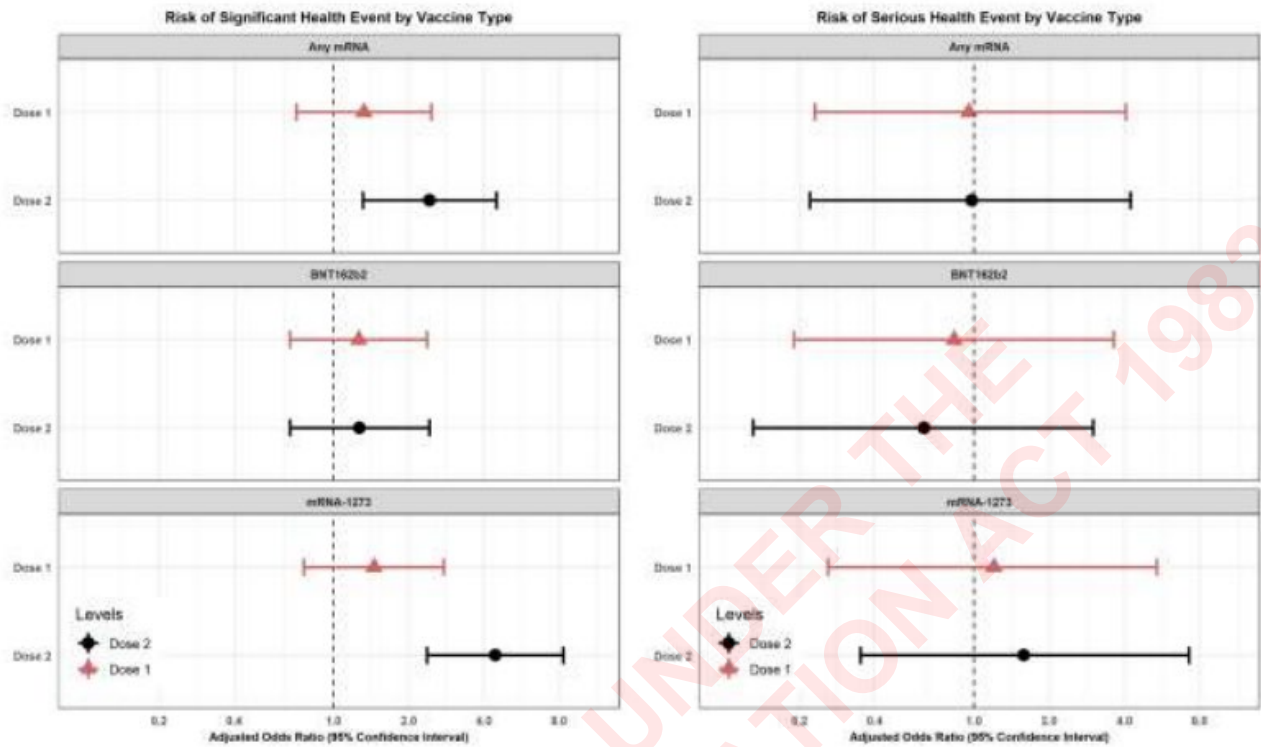
When comparing vaccinated pregnant and vaccinated non-pregnant people, significant AEFI rates (excluding injection site reactions) were consistently lower among pregnant people across all mRNA vaccine types and doses. Overall, 4.0% and 7.3% of pregnant people reported a significant AEFI after dose one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

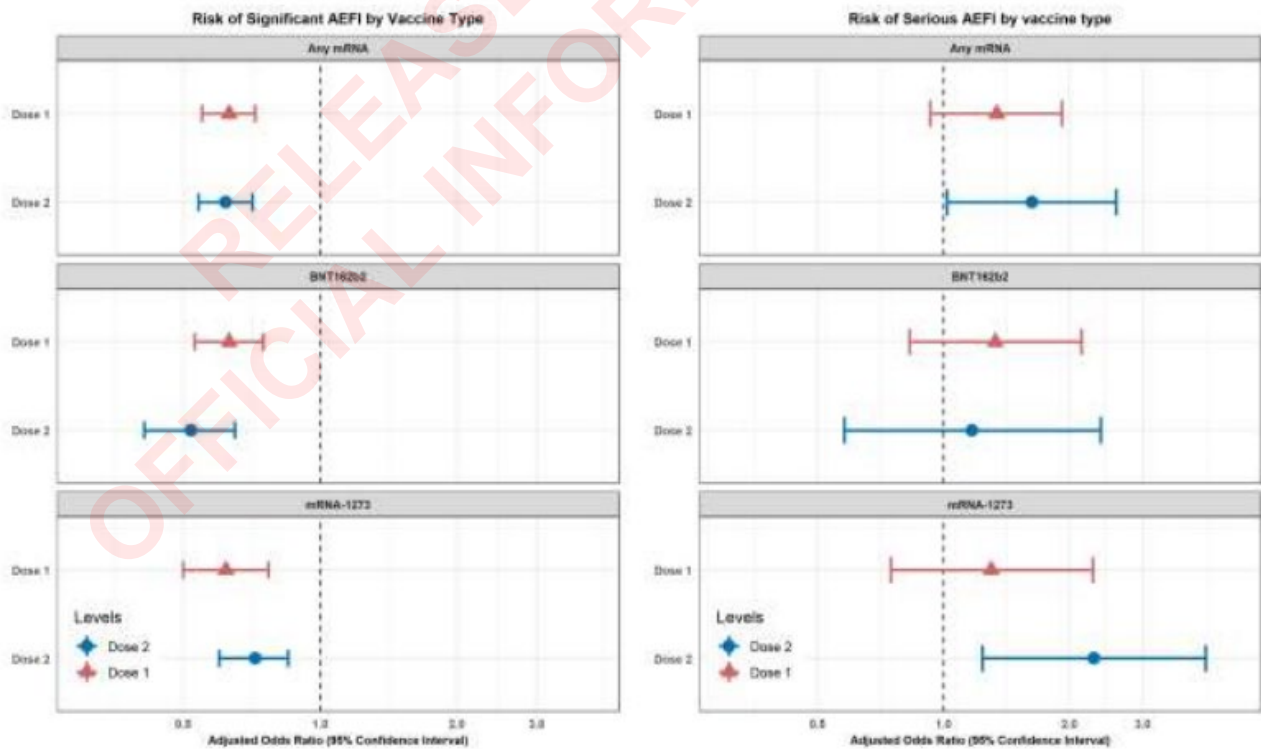
Limitations of this study include the potential for recall bias, lack of medical confirmation of serious events and relatively small sample size.

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]

(A)



(B)





*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)

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**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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# Memo

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

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## 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](http://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
<b>Inactivated vaccines</b>					
Seasonal TIV or H1N1 2009–2010 monovalent, non-adjuvanted 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	No safety concern identified	++++
Oil-in-water adjuvanted, monovalent H1N1 vaccines			Yes	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	Incidence not altered by pregnancy	Unknown for fetus; infants may develop significant morbidity and mortality.	No	No safety concern identified	++
Meningococcal conjugate vaccines			As part of mass campaigns.	No safety concern identified	+
<b>Live attenuated vaccines</b>					
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**

<b>Product name</b>	<b>Sponsor</b>	<b>TT50</b>
<i>BNT162b2 (mRNA)</i>		
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).

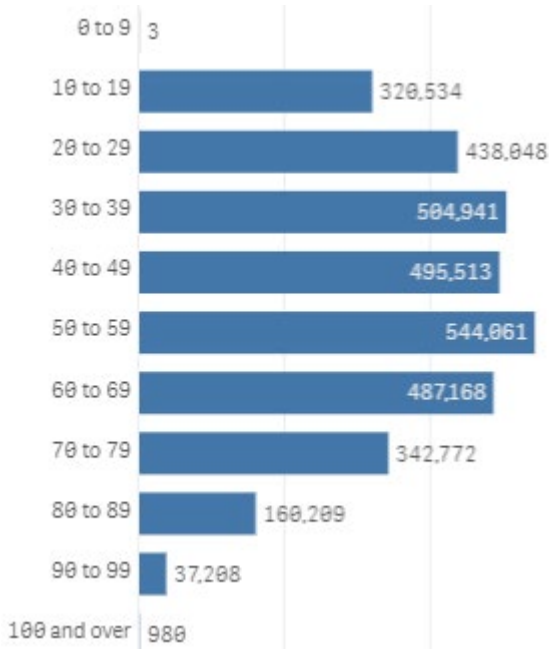
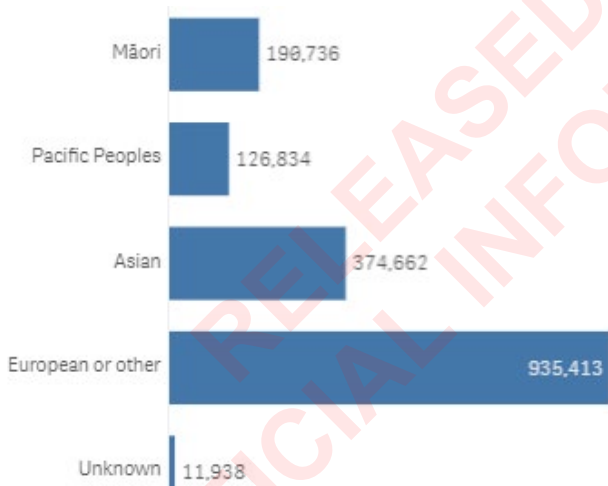


Figure 2: Vaccine doses administered to women of reproductive age (15-49 years) by ethnic group up to 21 October 2021. Source: COVID-19 Vaccination Events Qlik app, updated 21 October 2021 (accessed 21 October 2021).



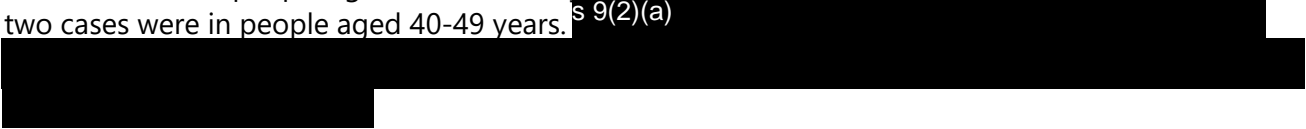
**SOURCE OF SAFETY CONCERN**

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)


Three cases were people aged under 20-29 years, eight cases were in people aged 30-39 years, and two cases were in people aged 40-49 years. s 9(2)(a)



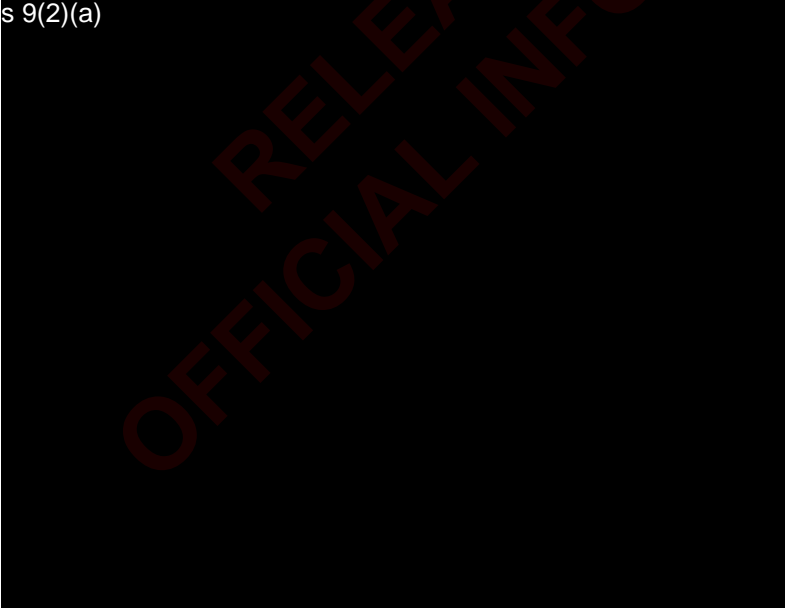
The remaining three cases describe exposure during pregnancy/dizziness, palpitations/foetal hypokinesia, and congenital abnormalities.

Annex 1 contains detailed information about the cases.

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



s 9(2)(a)



s 9(2)(a)

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s 9(2)(a)

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

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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***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 <sup>15-17‡</sup>	Not applicable	104
Stillbirth: ≥ 20 wk <sup>18-20</sup>	<1	1/725 (0.1)§
Neonatal outcome among live-born infants		
Preterm birth: <37 wk <sup>21,22</sup>	8-15	60/636 (9.4)¶
Small size for gestational age <sup>23,24  </sup>	3.5	23/724 (3.2)
Congenital anomalies <sup>25**</sup>	3	16/724 (2.2)
Neonatal death <sup>26††</sup>	<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-21<sup>st</sup> 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](http://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]

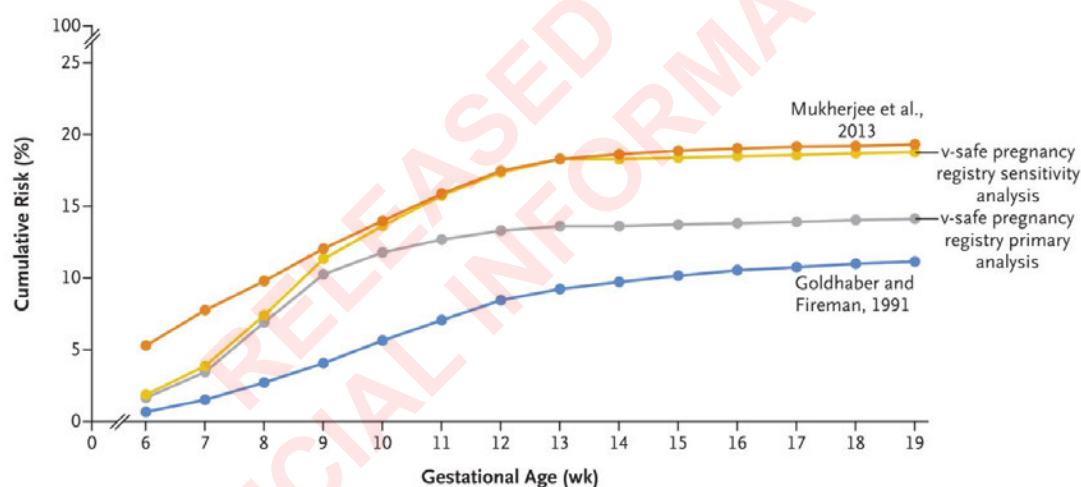
This research letter uses data from the Centres for Disease Prevention (CDC) v-safe pregnancy registry to determine the cumulative risk of spontaneous abortion from 6 to less than 20 weeks of gestation.

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) <sup>a</sup>	P value <sup>a</sup>
<b>Intrapartum complications</b>				
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
<b>Mode of delivery</b>				
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.

<sup>a</sup> 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). 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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