Australian Government
Department of Health

Surveillance and Targeted Review Stream (STRS) – Targeted Investigation Process (TIP) for vaccines

Medicines and Vaccines Investigation and Surveillance Section

TRIM reference:
D22-5024968

COVID-19 Vaccines and menstrual disorder

Date and Time completed	13/01/2022 4:00 PM

Summary

COVID-19 vaccines and menstrual disorders was referred to MAVIS for a Targeted Investigation Process (TIP) review following the vaccine event pair being raised at the Advisory Committee on Vaccines (ACV) meeting on 7/01/2022.

Menstrual irregularities occur in an estimated 14% to 25% of women of childbearing age. During the reproductive years, vaginal bleeding may be abnormal when menstrual periods are too heavy or too light, last too long, occur too often, or are irregular. Any vaginal bleeding that occurs before puberty or after menopause is considered abnormal until proven otherwise. Many things can cause irregular periods including: changing contraceptive methods; medications including antihypertensives, antiepileptics; lifestyle, including stress, extreme changes to weight, excessive exercise; polycystic ovary syndrome; hyperthyroidism or hypothyroidism; thickening of or polyps on the uterine lining; and uterine fibroids or malignancy.

Menstrual cyclicity is an overt sign of health and fertility. Although menstrual characteristics are not static, with variability month to month across an individual's lifespan, regularity is particularly important for those who rely on being able to predict their menstrual cycles to either achieve or avoid pregnancy. Variations in an individual's usual or regular menstrual cycle, even if these are not considered clinically (medically) significant, can cause unnecessary anxiety and stress.

There are 310 reports of menstrual disorders following Vaxzevria ChAdOx1-S (AZ), 1484 following Comirnaty (BNT162b2 [mRNA]) COVID-19 Vaccine (PF) and 107 following Spikevax (elasomeran) COVID-19 Vaccine (Spikevax) in the TGA's Adverse Event Management System (AEMS). No fatal outcomes have been reported.

The reporting rate of all menstrual disorders for all ages for AZ is 4.52 per 100,000 doses, for PF it's 9.85 per 100,000 doses and for Spikevax it's 10.71 per 100,000 doses. The reporting rate for PF and Spikevax is approximately double that of AZ for women of all ages. The reporting rate for premenopausal women for AZ is 19.65 per 100,000 doses, for PF it's 11.37 per 100,000 and for Spikevax it's 15.34 per 100, 000. The reporting rate for menopausal and postmenopausal women for AZ is 1.53 per 100,000 doses, for PF it's 2.87 per 100,000 and for Spikevax it's 0.53 per 100,000.

Disproportionate reporting was detected for menstrual disorders for PF in the 01 September to 31 October 2021 DPAR. Higher disproportionate reporting was identified specifically for irregular menstrual periods (menstruation delayed, menstruation irregular and polymenorrhea) and menstrual pain (Menstrual discomfort and Dysmenorrhea).

Menstrual disorders are not described in the Australian or international Product Information (PI) for AZ, PF or Spikevax.

The AZ sponsor's bimonthly safety summary report (MSSR) for data lock 01/08/2021 to 30/09/2021 included a review of post-menopausal haemorrhage. This review is a follow up to a previous review of cases of menstrual bleeding disorders which had excluded post-menopausal haemorrhage. The review concluded that there is no evidence currently to conclude that the reported cases of Post-menopausal Haemorrhage, can be causality related to AZ and that their earlier conclusion of no evidence that the reported cases of menstrual disorders could be causality related to AZ remains.

The PF sponsor's Periodic Safety Update Report (PSUR) for data lock 19/12/2021 to 18/06/2021 included a review of menstrual disorders. The sponsor's review of adverse events reported during a blinded placebo-controlled follow up period in the pivotal clinical trial did not reveal any imbalance in the incidence of reporting of menstrual cycle and uterine bleeding disorders between participants receiving BNT162b2 (Comirnaty) and those receiving placebo.

The review concluded that the sponsor analysis did not support a causal association between vaccination and menstrual alteration in women. There is compelling alternative explanation for menstrual irregularity during these pandemic times, as is supported by the lack of imbalance in a large placebo-controlled clinical trial with over 42000 participants, where approximately half were women. Additionally, there is neither significant literature nor post marketing data that supports a causal association.

On 6/01/2022, the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA) Coronavirus vaccine weekly summary of Yellow Card report included information about Menstrual disorders reported following vaccination against COVID-19. The MHRA is reviewing reports of suspected side effects associated with menstrual disorders (period problems) and unexpected vaginal bleeding following vaccination against COVID-19 in the UK. These reports are also being reviewed by independent experts on the Commission on Human Medicines' (CHM) COVID-19 Vaccines Benefit Risk Expert Working Group (EWG) and the Medicines for Women's Health Expert Advisory Group (MWHEAG). The rigorous evaluation completed to date does not support a link between changes to menstrual periods and related symptoms and COVID-19 vaccines. The MHRA states that the number of reports of menstrual disorders and vaginal bleeding is low in relation to both the number of people who have received COVID-19 vaccines to date and how common menstrual disorders are generally. The menstrual changes reported are mostly transient in nature and there is no evidence to suggest that COVID-19 vaccines will affect fertility.

On 17/11/2021, New Zealand's MedSafe published a Monitoring Communication about Menstrual disorders and unexpected vaginal bleeding following PF. They report that following investigation, there is no evidence to suggest a link between vaccination with PF and menstrual disorders.

s33 [redacted]

A published study by Edelman et al, funded by the National Institutes of Health (NIH), evaluating when COVID-19 vaccination is associated with menstrual cycle disturbances found no population-level meaningful change in menstrual cycle length associated with COVID-19 vaccination. The authors acknowledge that concerns about a possible association between COVID-19 vaccination and abnormal menstrual cycles may lead to vaccine hesitancy. They note that clinical trials of the current COVID-19 vaccines did not collect menstrual cycle outcomes post-vaccine, and that the lack of evidence limits the ability to address these concerns and to provide advice to individuals who menstruate about what to expect.

The Norwegian Institute of Public Health published initial results from a major study of the association between COVID-19 vaccines and menstrual changes in a cohort of 6000 women aged 18-30 years. **The study has not yet been peer-reviewed but has been submitted for preprint.** The study found that there was a high incidence of various menstrual changes among menstruating women prior to vaccination. After the first dose, 39.4 per cent of participants reported at least one change, and after the second dose, 40.9 per cent. It was reported that menstrual changes after the first dose were short-lived and returned to normal by the time

for vaccination with the second dose, approximately two to three months after vaccination with the first dose.

A study by Alvergne et al included analysis of a retrospective online survey conducted in March 2021 in the UK before there had been widespread media regarding potential impacts of COVID-19 vaccination on menstruation. 4,989 participants who were pre-menopausal and vaccinated were selected for this analysis. The study found that following vaccination for COVID-19, menstrual disturbance occurred in 20% of individuals in a UK sample. Out of 33 variables investigated, smoking and a previous history of SARS-CoV-2 infection were found to be risk factors, while using oestradiol-containing contraceptives was found to be a protective factor. **The paper is in preprint and has not been peer-reviewed.**

Recommendations

It is the recommendation of this review for the TGA to:

1. **Publish an article on this topic in the weekly COVID-19 vaccine weekly safety report on the TGA website**
2. **VERA to consider referral to ATAGI for similar messaging, if appropriate**
3. **Return the signal to routine pharmacovigilance monitoring.**

Priority

Medium

MO5/Stream Lead/MaVIS Issues Meeting Advice

DISCLAIMER: The purpose of this report is to provide a targeted assessment (at a point in time) of the described vaccine-event pair to assist with triage of workflow. It does not constitute a full evaluation nor a regulatory decision.

1. List of abbreviations

Abbreviation	Meaning
ACCESS	Australia-Canada-Singapore-Switzerland-United Kingdom (consortium)
ADR/AE	Adverse Drug Reaction / Adverse Event
AEFI	Adverse Event Following Immunisation
AEMS	Adverse Event Management System
AESI	Adverse Event of Special Interest
AIR	Australian Immunisation Register
ARTG	Australian Register of Therapeutic Goods
ATAGI	Australian Technical Advisory Group on Immunisation
ATC	Anatomical Therapeutic Chemical (classification system)
AZ	VAXZEVRIA ChAdOx1-S, previously COVID-19 Vaccine AstraZeneca
CMI	Consumer Medicine Information
COVID-19	Coronavirus disease 2019
DHCPL	Dear Healthcare Professional Letter
EMA	European Medicines Agency (European Union)
FDA	Food and Drug Administration (United States)
GACVS	Global Advisory Committee on Vaccine Safety
IC	Information Component
ICMRA	International Coalition of Medicines Regulatory Authorities
IPMST	International Post Market Surveillance Teleconference
MaVIS	Medicines and Vaccines Investigation and Surveillance
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency (United Kingdom)
MSSR	Monthly Safety Summary Report
MSU	Medicines Safety Update
NCIRS	National Centre for Immunisation Research and Surveillance
O/E	Observed vs. Expected (analysis)

PF	COMIRNATY (BNT162b2 [mRNA]) COVID-19 Vaccine Pfizer
PI	Product Information
PRAC	Pharmacovigilance Risk Assessment Committee
PRR	Proportional Reporting Ratio
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
RMP	Risk Management Plan
ROS	Regulatory Outcomes Stream
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SPC/SmPC	Summary of Product Characteristics
SSR	Safety Summary Report
STRS	Surveillance and Targeted Review Stream
TIP	Targeted Investigation Process
VERA	Vaccine Epidemiology and Rapid Assessment
VSIG	Vaccine Safety Investigation Group
WHO-UMC	World Health Organisation – Uppsala Monitoring Centre

DELETE: Please list all the abbreviations used in your report in the table provided above. Some examples have been included in the table.

2. Vaccine information

Indication(s)	For VAXZEVRIA ChAdOx 1-S (AZ): Provisional approval for active immunisation of individual ≥ 18 years old for the prevention of COVID-19 caused by SARS-CoV-2. The TGA provisionally approved it for use in Australia on 15 February 2021. For COMIRNATY (BNT162b2 [mRNA]) COVID-19 Vaccine Pfizer (PF): Provisional approval for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 5 years of age and older. The TGA provisionally approved it for use in Australia on 25 January 2021 (for 16 years and over), 22 July 2021 (for 12 years and over), 26 October 2021 (booster dose for 18 years and over), and 3 December 2021 (for 5 years and over). For SPIKEVAX (elasomeran) COVID-19 VACCINE (Spikevax): Provisional approval for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older. The TGA provisionally approved it for use in Australia on 9 August 2021 (for 18 years and over), 3 September 2021 (for 12 years and over), and 7 December 2021 (booster dose for 18 years and over). For COVID-19 VACCINE JANSSEN Ad26.COV2.S (Janssen): Provisional approval for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18

	years of age and older. The TGA provisionally approved it for use in Australia on 25 June 2021.
Vaccine roll-out status	There are three COVID-19 vaccines in the national rollout. AZ is approved for use in people aged 18 years and over. The TGA provisionally approved it for use in Australia on 15 February 2021. The Australian Technical Advisory Group on Immunisation (ATAGI) recommends AZ for people: • **aged 60 and over** • **aged 18 to 59 in outbreak areas**, if they do not have immediate access to PF or Spikevax. If you are aged 18 to 59, you can choose to get protected with AZ: • following an assessment by a qualified health professional • if you provide verbal or written consent. PF is approved for use in people aged 5 years and over. The TGA provisionally approved PF for use in Australia on 25 January 2021 (for 16 years and over), 22 July 2021 (for 12 years and over) and 5 December 2021 (for 5 years and over). PF is currently available for all people aged 5 years and over. Appointments for children aged 5 to 11 years started from 10 January. Spikevax is approved for use in people aged 12 years and over. The TGA provisionally approved it for use in Australia on 9 August 2021 (for 18 years and over) and 3 September 2021 (for 12 years and over). In Australia's vaccine rollout, Spikevax is now available for people aged 12 years and over. PF and Spikevax are approved by the TGA and recommended by ATAGI as a COVID-19 booster dose. You can have PF or Spikevax as a booster dose regardless of which vaccine you had for your first 2 doses. You can also receive AZ if you: • can't have PF or Spikevax for medical reasons • had 2 doses of AZ previously.
Mechanism of action	<u>For COVID-19 vaccines:</u> • AZ ChAdOx 1-S is a recombinant replication-defective chimpanzee adenovirus ChAdOx1, carrying a gene encoding the SARS-CoV-2 spike (S) surface glycoprotein. Following administration, the S glycoprotein is expressed locally, stimulating neutralising antibody and cellular immune responses. • PF comprises a nucleoside-modified messenger RNA (modRNA) encoding the viral spike glycoprotein (S) of SARS-CoV-2. The RNA is encapsulated in lipid nanoparticles (LNPs), which enables entry into host cells, expression of the S protein, and elicitation of both antibody and cellular immune responses. • SPIKEVAX contains messenger ribonucleic acid (mRNA) encapsulated in lipid nanoparticles. The mRNA encodes for the full-length SARS-CoV-2 spike protein modified with 2 proline substitutions within the heptad repeat 1 domain (S-2P) to stabilise the spike protein into a prefusion conformation. Following administration, the lipid nanoparticle deliver the mRNA sequence into cells for translation, expression of the viral spike protein, and elicitation of both antibody and cellular immune responses.

	• Janssen is a recombinant replication-incompetent human adenovirus type 26 vector that encodes a SARS-CoV-2 spike (S) glycoprotein. Following administration, the S glycoprotein is transiently expressed, stimulating neutralising and other functional S-specific antibodies, as well as cellular immune responses.

3. Adverse event information

Signal Source	COVID-19 vaccines and menstrual disorders was referred to MAVIS for a targeted review following the vaccine event pair being raised at the Advisory Committee on Vaccines (ACV) meeting on 7/02/2022. [TRIM: D22-5024182] Any TIP referrals and/or related information can also be found at E21-419218.
AESI status	Menstrual disorders are not identified as adverse events of special interest (AESI). The AESI list for COVID-19: • VERA's AESI resources – E21-366692 • Vaccine Surveillance Section's (pre-MaVIS) AESI list – D20-3595626.
AEFI	Information taken from Targeted Review: *Vaxzevria (previously COVID-19 Vaccine AstraZeneca) ChAdOx1-S and Comirnaty (BNT162b2[mRNA]) COVID-19 vaccine and menstrual disorders* which was completed 20/08/2021 [TRIM D21-2947788] Menstrual irregularities occur in an estimated 14% to 25% of women of childbearing age[1]. During the reproductive years, vaginal bleeding may be abnormal when menstrual periods are too heavy or too light, last too long, occur too often, or are irregular. Any vaginal bleeding that occurs before puberty or after menopause is considered abnormal until proven otherwise. Many things can cause these changes including: • Changing contraceptive methods • Medications including antihypertensives, antiepileptics • Lifestyle, including stress, extreme changes to weight, excessive exercise, • Polycystic ovary syndrome • Hyperthyroidism or hypothyroidism • Thickening of or polyps on the uterine lining • Uterine fibroids or malignancy. Menstrual cyclicity is an overt sign of health and fertility. Although menstrual characteristics are not static, with variability exists month to month across an individual's lifespan, regularity is particularly important for those who rely on being able to predict their menstrual cycles to either achieve or avoid pregnancy. Variations in an individual's usual or regular menstrual cycle, even if these are not considered clinically (medically) significant, can cause unnecessary anxiety and stress. There are potentially more long terms risks to health depending on the particular menstrual disorder experienced. For example, untreated menorrhagia (heavy menstrual bleeding) affects about one in five women and is a common problem in

[1] Whitaker, L., & Critchley, H. O. D. (2016). Abnormal uterine bleeding. *Best Practice & Research Clinical Obstetrics & Gynaecology, 34,* 54–65. Retrieved December 2, 2016, from http://www.sciencedirect.com/science/article/pii/S1521693415002266 [TRIM D21-2995095]

the 30-50 year age group[2]. It is a common cause of iron deficiency anaemia in females.[3] It negatively affects quality of life and is associated with financial loss, decreased productivity, poor health (including stress and anxiety), and increased use of health care resources[4].

The most common cause of postmenopausal bleeding is endometriosis, however 10% of women with postmenopausal bleeding will be found to have endometrial cancer. In these cases postmenopausal bleeding is an early warning sign that leads women to seek medical advice.[5]

Magnitude of signal

TGA DPAR [TRIM D22-5027565]

DPAR - 1/09/2021 to 31/10/2021

The menstrual disorder MedDRA preferred terms (PTs) flagged for PF only. In particular, higher disproportionate reporting of irregular menstrual periods (Intermenstrual bleeding, menstruation delayed and menstruations irregular) and menstrual pain (Menstrual discomfort and Dysmenorrhea) were identified. Disproportionate reporting of Menstrual disorder was also identified. The reporting of this generic PT, doesn't identify the specific menstrual issue being reported. AZ and Spikevax did not flag.

DPAR for PF only.					
PT	**Number of cases**	**PRR**	**PRR LCI**	**IC**	**IC LCI**
Abnormal uterine bleeding	3	4.14	0.69	0.94	-1.13
Amenorrhoea	30	6.9	3.53	1.39	0.78
Dysmenorrhea	137	11.82	8.04	1.6	1.31
Heavy Menstrual bleeding	309	8.98	7.14	1.52	1.33
Intermenstrual bleeding	145	12.13	8.31	1.6	1.33
Menometrorrhagia	3	8.28	0.86	1.16	-0.91
Menstrual discomfort	5	13.8	1.61	1.39	-0.17
Menstrual disorder	775	12.36	10.49	1.62	1.5
Menstruation delayed	46	14.11	6.91	1.62	1.13
Menstruation irregular	187	10.75	7.83	1.57	1.33

DPAR – 1/07/2021 to 31/08/2021.

The PTs flagged for PF apart for postmenopausal haemorrhage which flagged for AZ. In particular, higher disproportionate reporting was identified for irregular menstrual periods (menstruation delayed, menstruation irregular and polymenorrhea).

AZ flagged for postmenopausal haemorrhage only (**bolded in table below**). Spikevax did not flag in the DPAR.

DPAR for PF and one AZ / Event pair (in bold in last row of table)					
PT	**Number of cases**	**PRR**	**PRR LCI**	**IC**	**IC LCI**
Amenorrhoea	8	3.65	1.41	1.15	-0.06

[2] Jean Hailes Heavy Menstrual Bleeding – fact sheet – updated May 2019 https://assets.jeanhailes.org.au/heavy_menstrual_bleeding.pdf?_ga=2.70192912.1846493863.1629424949-62988700.1628555415 [TRIM D21-2998523]

[3] Apgar BS, Kaufman AH, George-Nwogu U, Kittendorf A. Treatment of menorrhagia. Am Fam Physician. 2007 Jun 15;75(12):1813-9. PMID: 17619523. [TRIM D21-2997473]

[4] Wouk N, Helton M. Abnormal Uterine Bleeding in Premenopausal Women. Am Fam Physician. 2019 Apr 1;99(7):435-443. PMID: 30932448. [TRIM D21-2997572]

[5] Brand AH, The woman with postmenopausal bleeding. Aust. Fam Physician. 007 March Vol. 36, No. 3. [TRIM D21-2999928]

Dysmenorrhea	40	7.47	4.44	1.68	1.15
Heavy Menstrual bleeding	107	6.47	4.77	1.63	1.31
Menstrual disorder	257	11.36	8.96	1.9	1.69
Menstruation delayed	16	10.96	4.29	1.78	0.94
Menstruation irregular	74	10.49	6.83	1.85	1,47
Polymenorrhoea	23	11.82	5.29	1.84	1.14
Postmenopausal haemorrhage	**27**	**3.46**	**1.92**	**0.99**	**0.34**

TGA vaccine reporting rates of all Menstrual Disorder PTs for females of all ages up to 11/01/2022

The total reporting rate of menstrual disorders is almost twice for PF and Spikevax than the reporting rate for AZ.

Vaccine	Number of Doses	Number of Reports	Reporting Rate per 100,000 doses
AZ	6770529	306	4.52
PF	14787906	1457	9.85
Spikevax	998605	107	10.71

TGA reporting rates for females above and below 50 years of age.

The age range is used to show the potential differences between pre- and post-menopausal women reporting rates. The average age of menopause for women in Australia is 51-52 years[6].

The reporting rate for women under 50 years for AZ is almost twice that for PF.

Vaccine	Age Range	Number of Doses	Number of Reports*	Reporting Rate per 100,000 doses
AZ	<50 years	1002346	197	19.65
	≥50 years	5768183	88	1.53
PF	<50 years	10751463	1222	11.37
	≥50 years	4036443	116	2.87
Spikevax	<50 years	619193	95	15.34
	≥50 years	379412	2	0.53

* Excludes reports where the age is not reported:

- 21 reports for AZ
- 119 reports for PF
- 10 reports for Spikevax

Source for information used to calculate reporting rates

Following a search on MedDRA a list of 18 preferred terms (PTs) were identified to describe a range of menstrual bleeding and menstrual cycle disorders [TRIM D22-5028589].

MedDRA Preferred Terms	Definitions – where needed
Heavy menstrual bleeding	Excessive menstrual blood loss which interferes with a woman's physical, social, emotional and/or material quality of life

[6] Jean Hailes Menopause – fact sheet – updated September 2018 https://www.jeanhailes.org.au/resources/menopause-fact-sheet TRIM D21-2989287

	Menometrorrhagia	Excessive uterine bleeding, both at the usual time of menstrual periods and at other irregular intervals
	Polymenorrhagia	Excessive or frequent menstruation
	Polymenorrhoea	Menstrual cycle that is shorter than 21 days
	Menstrual discomfort	
	Amenorrhoea	An abnormal absence of menstruation
	Hypomenorrhoea	Decreased menstrual flow
	Menstruation delayed	
	Oligomenorrhoea	Irregular and inconsistent menstrual blood flow
	Retrograde menstruation	Menstrual flow moves in the wrong direction
	Premenstrual syndrome	Physical and emotional symptoms that some women experience in the lead up to menstruation.
	Premenstrual pain	
	Menstruation irregular	
	Menstrual disorder	
	Intermenstrual bleeding	Vaginal bleeding at any time during the menstrual cycle other than during normal menstruation.
	Dysmenorrhoea	Painful, cramping sensation in the lower abdomen or back associated with menstrual periods
	Abnormal uterine bleeding	
	Postmenopausal haemorrhage	Vaginal bleeding after menstrual cycles have ceased due to menopause.

The number of doses is taken from the Australian Immunisation Register (AIR) which was pulled from QLIK on 11/01/2022 - data up to and including 10/01/2022 [TRIM D22-5028729]

The number of AEFI reports received by the TGA and entered into the TGA's Adverse Event Management System (AEMS) was pulled from QLIK on 11/01/2022 – data up to and including 10/01/2022
AZ Reports [TRIM: D22-5029226]
PF reports [TRIM: D22-5030843]
Spikevax reports [TRIM D22-5030827]

No. of AEFI reports

QLIK searches on 12/01/2022 using the default bookmark and the 18 PTs identified in the MedDRA search were conducted separately for AZ, PF and Spikevax.

The search for AZ identified 310 case reports. The PCDs for the AZ are filed in TRIM: D22-5037234.

The search for PF identified 1484 case reports. The PCDs for the PF are filed in TRIM: D22-5037685 (Mar-July); D22-5037692 (Aug); D22-5037695 (Sept); D22-5037702 (Oct); D22-5037706 (Nov); D22-5037712 (Dec); D22-5037717 (Jan 2022).

The search for Spikevax identified 107 case reports. The PCDs for the Spikevax are filed in TRIM: D22-5037728

A comparison of the numbers of PTs reported by vaccine. Note that more than one PT can be reported in each report

Adverse Event PT	AZ	PF	Spikevax
Menstrual disorder	211	1281	106
Heavy Menstrual Bleeding	107	516	40
Menstruation Irregular	49	338	26
Intermenstrual bleeding	37	209	17
Dysmenorrhoea	31	201	22
Polymenorrhoea	15	99	3
Menstruation delayed	11	99	6
Postmenopausal haemorrhage	39	58	-
Amenorrhoea	9	62	2
Oligomenorrhoea	12	63	11
Hypomenorrhoea	-	4	-
Menstrual discomfort	1	9	1
Premenstrual pain	-	1	-
Abnormal uterine bleeding	2	5	1
Menometrorrhagia	1	9	1
Premenstrual syndrome	2	2	-

A comparison of the number of reports submitted by age group for each vaccine

	18-44 years			45-64			65-74			75 and above			Unknown		
Vaccine	AZ	PF	SV*	AZ	PF	SV	AZ	PF	SV	AZ	PF	SV	AZ	PF	SV
Number of Reports	162	1010	75	114	321	16	13	2	-	-	3	-	21	119	10

*SV=Spikevax

PF - 29 reports in the adolescent age group – (12-17 years)
Spikevax – 6 reports in the adolescent age group – (12-17 years)

The management of events reported for each Vaccine

Management of events reported	AZ (310 reports)	PF (1484 reports)	Spikevax (107 reports)
GP assessment	44	191	7
Helpline	4	13	1
Hospital admission	4	16	1
Hospital ED	20	60	3
None	5	22	3
Self	52	235	21
Unknown	13	104	14
Not reported	168	947	59

The Outcome of events reported for each vaccine.

Outcome reported at time of reporting	AZ Vaccine (310 reports)	PF vaccine (1484 reports)	Spikevax (107 reports)
Not recovered/ongoing	150	844	71
Recovered	68	246	11
Recovered with sequelae	4	9	-
Recovering	38	158	12
Unknown	50	227	13
Fatal	-	-	-

AEFI by dosage and vaccine administered

More AEFIs were reported following the first dose of both vaccines. However, there are many reports where the dose number was not provided.

Doses	AZ	PF	Spikevax
First dose	142	514	46
Second dose	34	423	17
Unknown	134	547	44

Summary of AEFI reports

A total of 1901 AEFI reports have been received by the TGA of which 310 are for AZ, 1484 are for PF and 107 are for Spikevax.

A high-level review of the reports was conducted due to the large number of reports identified in the QLIK search. 18 MedDRA PTs been used to identify relevant reports for this review which covers a very broad range of menstrual disorders with varying causalities that traverse a wide range of age groups. Many have the reports include more than one PT and don't include any or enough information to undertake meaningful analysis.

A review of s22

Duplicate reports ADR 610587 and ADR 622017: a 71 year old s22 s22

ADR 735075: a 57 year old s22 s22

ADR 639488: a 56 year old s22 s22

A review of s22

ADR 660367: a 38 year old s22 s22

A review of s22

ADR	Age	TTO	Coding	Narrative
555465	38	s22	Heavy Menstrual Bleeding Menstruation Irregular Vaginal haemorrhage	s22
576947	40	s22	Heavy Menstrual bleeding **ITP**	

				s22
588762	36	s22	Blood fibrinogen decreased Haemoglobin decreased Headache Heavy Menstrual bleeding Menstrual disorder Petechiae RBC count decreased Thrombocytopenia Thrombocytopenic purpura WBC count increased	
595580	39	s22	Headache Injection site pain Menstrual disorder Muscular weakness Orthostatic hypotension Pain in extremity Vertigo Vestibular neuronitis	s22
636523	-	s22	Heavy Menstrual bleeding Menstrual disorder	
641062	41		Dyspnoea Injection site Reaction Menstrual disorder	

				Pericardial effusion preicarditis
	642057	26	s22	Dysmenorrhoea Heavy Menstrual bleeding Intermenstrual bleeding Menstrual disorder
	648202	40	s22	GBS Heavy mensutrual bleeding Menstrual disorder oligomenorrhoea
	649220	20	s22	Amenorrhoea Chest pain Dyspnoea Menstrual disorder tachycardia
	649564	44	s22	Heavy Menstrual bleeding Hyperplasia Menstrual disorder Menstruation irregular olimenorrhoae

s22

				s22
	664009	34	s22	Arthralgia Back pain Chest pain Cough C-reactive protein increased Cytokine abnormal Decreased appetite Dysphagia Electric shock sensation Erythromelalgia Facial spasm Fatigue Feeling abnormal Fidrin D dimer increased Flushing Genito-pelvic pain/ penetration Headache Menstrual disorder Menstruation irregular Muscle spams Vision blurred Tinnitus Tremor Tachycardia petechiae
	665322	47	s22	Heavy menstrual bleeding Menstrual disorder Migraine polymenorrhoea
	666179	27	s22	Chest Pain Fibrin D dimer increased Injection site reaction Menstrual disoder

				s22
671031	28	s22	Anaemia Chest pian Dyspnoea Haemoglobin decreased Heavy menstrual bleeding Menstruation irregular palpitations	
675067	33	s22	Cardiomegaly Chest pain Dyspnoea Fatigue Fibrin D dimer increased Menstrual disorder Nausea Platelet count decreased pyrexia	

4. Regulatory surveillance

Local, including: **PI, Sponsor's PSUR/MSSR, and applicable clinical guidance**	**Product Information (PI)**
	The Australian Product Information (PI) for AZ was updated on 04/01/2022. Menstrual disorders are not listed. [TRIM D22-5031612] The PIs for PF were updated on 23/12/2021. Menstrual disorders are not listed [TRIM D22-5031646 and D22-5031665] The PI for Spikevax was updated on 9/12/2021. Menstrual disorders are not listed. [TRIM D22-5031693]
	Applicable clinical guidance
	The *Clinical Guidance for COVID-19 vaccines providers* was last updated on 6/01/2022 (accessed on 11/01/2022). Menstrual disorders are not referenced in the clinical guidance document. It is available at: https://www.health.gov.au/initiatives-and-programs/covid-19-vaccines/advice-for-providers/clinical-guidance
	Sponsor's PSUR/MSSR/SSR
	AZ

The AZ bimonthly Monthly SSR – 1/10/2021 to 30/11/2021 [TRIM D21-3455300]
The MSSR does not identify Menstrual disorders as an issue for review.

The AZ bimonthly MSSR – 1/08/2021 to 30/09/2021 [TRIM D21-3260098]
Section 7. Health Authority Requests of the MSSR identified Post-menopausal haemorrhage as a topic for review, requested by the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC).
Section7.6 Post-menopausal haemorrhage
This review is a follow up to the previous review of cases of menstrual bleeding disorders undertaken in the 01/06/2021 to 31/07/2021 MSSR. PRAC has requested a review cases of post-menopausal haemorrhage which was excluded from the earlier review and an reassessment if the addition of this PT changes the sponsor's previous analysis and conclusions on this topic.
Conclusion:
Based on the review of the cumulative data, and cases reported to the company, it is AstraZeneca's view that there is no evidence currently to conclude that the reported cases of Post-menopausal Haemorrhage, can be causality related to vaccination with COVID-19 VACCINE ASTRAZENECA. Most of the cases reported with this PT lack of information and no trend has being seen. This additional analysis does not *change our previous conclusions provided in the previous MSSR related to reports of menstrual disorders where all the*
following terms were analysed: MedDRA High Level Terms (HLT): Menstruation and uterine bleeding NEC, Menstruation with decreased bleeding, Menstruation with increased bleeding and the MedDRA PTs: Vaginal haemorrhage, and Uterine haemorrhage.

The AZ Periodic Safety Update Report (PSUR) 29/12/2020 to 28/06/2021 [TRIM D21-3087786]
The PSUR does not identify Menstrual disorders as an issue for review

PF
The PF MSSR 01/10/2021 to 28/10/2021 [TRIM D21-3349826
The MSSR does not identify Menstrual disorders as an issue for review.

The PF MSSR 01/09/2021 to 30/09/2021 [TRIM D21-3234082]
The MSSR does not identify Menstrual disorders as an issue for review

The PF PSUR 19/12/2021 to 18/06/2021 [TRIM D21-3029287]
Section 15. Overview of signals: New, ongoing or closed
Section 15.10 Menstrual Disorders
The MAH is requested to include in this PSUR review a separate post-marketing cases evaluation of the cases reporting a menstrual disorder, which should also include a sub-analysis of cases divided between post-menopausal cases and menstrual disorder cases.
Conclusion
Recent studies have demonstrated that a sizable proportion of women have experienced menstrual cycle disturbances because of the COVID-19 pandemic. In one study, almost half of the women reported periods that were heavier and painful compared to before the pandemic. These are likely to be associated with psychological distress and stress related to the pandemic, weight gain, longer working hours, and dietary changes. Stress and stress hormones have an inhibitory effect on the GnRH release from the hypothalamus.

A review of adverse events reported during the blinded placebo-controlled follow-up period in the pivotal clinical trial did not reveal any imbalance in the incidence of reporting of menstrual cycle and uterine bleeding disorders between participants receiving BNT162b2 and those receiving placebo.

	Many of the cases retrieved from the search of the safety database were significantly confounded by their past/concurrent medical conditions or lack of reported clinical information with which to assess a potential relationship. In aggregate, most of the reports (n = 1886, 77.7%) occurred in women between 18 and 50 years of age, with most of these cases reporting a prior history of suppressed lactation, contraceptive usage, or previous history of menstrual abnormality. *Analysis of serious cases showed that 3.4% of all serious cases reported menstrual irregularities that resulted in hospitalization. The majority of these few cases were confounded by relevant medical history while others had limited information.* *The few numbers of cases of thrombocytopenia associated with menorrhagia suggests that thrombocytopenia, regardless of etiology, is not a commonly co-reported event with metrorrhagia following COVID-19 vaccination with BNT162b2.* *Overall, this analysis does not support a causal association between vaccination and menstrual alteration in women. There is compelling alternative explanation for menstrual irregularity during these pandemic times, as is supported by the lack of imbalance in a large placebo-controlled clinical trial with over 42000 participants, where approximately half were women. Additionally, there is neither significant literature nor post marketing data that supports a causal association. Routine monitoring will continue.* **Spikevax** The Spikevax MSSR 01/11/2021 to 30/11/2021 [TRIM D21-3470427] The MSSR does not identify Menstrual disorders as an issue for review. The Spikevax MSSR 01/10/2021 to 31/10/2021 [TRIM D21-3352060] The MSSR does not identify Menstrual disorders as an issue for review.
US FDA	**Label** PF drug label was last updated 03/03/2022. Menstrual disorders are not listed. [TRIM D22-5032369] Spikevax drug label was last updated 19/11/2021. Menstrual disorders are not listed. [TRIM D22-5032371] Janssen drug label was last updated 14/12/2022. Menstrual disorders are not listed. [TRIM D22-5032374] **Relevant regulatory action** The FDA Advisory Committee on Immunisation Practices (ACIP) recommendations published 5 November, 24 September and 13 August were reviewed. Menstrual disorders were not mentioned: *www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/covid-19.html* The Summary Minutes for the 167th FDA Vaccines and Related Biological Products Advisory Committee (VRBPAC) 26 October 2021 meeting were reviewed. Menstrual disorders were not mentioned: *Vaccines and Related Biological Products Advisory Committee October 26, 2021 Meeting Summary Minutes (fda.gov)*
National Institutes of Health (NIH)	On 6/01/2022 the National Institutes of Health have published the findings from a study: Women receiving one dose of a COVID-19 vaccine during a single menstrual cycle had an increase in cycle length of nearly one day, compared to unvaccinated women, according to a study funded by the National Institutes of Health. The increase in cycle length—a longer time between bleeding—was not associated with any change in the number of days of menses (days of bleeding). The study appears in *Obstetrics & Gynecology*.

	The authors, led by Alison Edelman, M.D., M.P.H., of Oregon Health & Science University, Portland, noted that menstrual cycles typically vary a small amount from month to month, and the increase they saw was well within the range of normal variability. They added that additional research is needed to determine how COVID-19 vaccination could potentially influence other menstrual characteristics, such as associated symptoms (pain, mood changes, etc.) and characteristics of bleeding (including heaviness of flow). [TRIM D22-5036632] More information about the article is in the Literature section of the TIP.
EU EMA	**Summary of Product Characteristics (SmPC)**
	Comirnaty SmPC was last updated 6/12/2021 Menstrual disorders are not listed. [TRIM D22-5033074] Vaxzevria SmPC was last updated 24/11/2021 Menstrual disorders are not listed. [TRIM D22-5033087] Spikevax SmPC was last updated 9/12/2021 Menstrual disorders are not listed. [TRIM D22-5033127]
	Relevant regulatory action
	The Pharmacovigilance Risk Assessment Committee (PRAC) meeting highlights for the meetings on 29 November – 2 December, 25-28 October and 27-20 September were reviewed. Menstrual were not discussed: https://www.ema.europa.eu/en/committees/prac/prac-agendas-minutes-highlights#meeting-highlights-section EMA Comirnaty safety update 6/12/2021 - Menstrual disorders not mentioned. [TRIM D22-5033217] EMA Vaxzevria safety update 6/12/2021- Menstrual disorders not mentioned. [TRIM D22-5033229] EMA Spikevax safety update 6/12/2021 - Menstrual disorders not mentioned. [TRIM D22-5033240]
UK MHRA	**Summary of Product Characteristics (SPC)**
	Comirnaty SPC was last updated 22/12/ 2021. Menstrual disorders are not listed. [TRIM D22-5033956] Vaxzevria SPC was last updated 13/12/2021. Menstrual disorders are not listed. [TRIM D22-5033346] Spikevax SPC was last updated 23/12/2021. Menstrual disorders are not listed. [TRIM D22-5033330]
	Relevant regulatory action
	MHRA Coronavirus vaccine - weekly summary of Yellow Card reporting; Updated 6/01/2022 [TRIM D22-5033951] The report includes the following information about Menstrual Disorders: ***Menstrual disorders (period problems) and unexpected vaginal bleeding*** *The MHRA is reviewing reports of suspected side effects of menstrual disorders (period problems) and unexpected vaginal bleeding following vaccination against COVID-19 in the UK. These reports are also being reviewed by the independent*

	experts of the Commission on Human Medicines' COVID-19 Vaccines Benefit Risk Expert Working Group and the Medicines for Women's Health Expert Advisory Group. The rigorous evaluation completed to date does not support a link between changes to menstrual periods and related symptoms and COVID-19 vaccines. *A total of 45,574 suspected reactions relating to a variety of menstrual disorders have been reported after all three of the COVID-19 vaccines including heavier than usual periods, delayed periods and unexpected vaginal bleeding. These suspected reactions have been reported in 35,567individual Yellow Card reports (as each report may contain more than one suspected reaction). This is following approximately 51.1 million COVID-19 vaccine doses administered to women up to 22 December 2021. The number of reports of menstrual disorders and vaginal bleeding is low in relation to both the number of people who have received COVID-19 vaccines to date and how common menstrual disorders are generally.* *The menstrual changes reported are mostly transient in nature. There is no evidence to suggest that COVID-19 vaccines will affect fertility and your ability to have children.* *Whilst uncomfortable or distressing, period problems are extremely common and stressful life events can disrupt menstrual periods. Changes to the menstrual cycle have also been reported following infection with COVID-19 and in people affected by long-COVID. General advice about period problems and/or unexpected vaginal bleeding is available from the NHS website. It is important that anyone experiencing changes to their periods that are unusual for them, persist over time, or has any new vaginal bleeding after the menopause, following COVID-19 vaccination, should contact their doctor. Anyone presenting with menstrual disorders and/or unexpected vaginal bleeding following COVID-19 vaccination should be treated according to clinical guidelines for these conditions, as usual.* *The MHRA continues to closely review reports of suspected side effects of menstrual disorders and unexpected vaginal bleeding.*
Health Canada	**Product Monograph (PM)** Vaxzevria PM was last updated 19/11/2021 Menstrual disorders are not listed. [TRIM D22-5034007] Comirnaty PM was last updated 19/11/2021 Menstrual disorders are not listed. [TRIM D22-5034045] Spikevax PM was last updated 23/12/2021. Menstrual disorders are not listed. [TRIM D22-5034071] **Relevant regulatory action** Health Canada COVID-19 vaccine safety weekly report 7/01/2022. Menstrual disorders are not mentioned. [TRIM D22-5034218]
NZ Medsafe	**Datasheet** Comirnaty data sheet was last updated 16/12/2022. Menstrual disorders are not listed. [TRIM D22-5034247] Vaxzevria data sheet was last updated 5/11/2021. Menstrual disorders are not listed. [TRIM D22-5034279] **Relevant regulatory action** MedSafe COVID-19 Vaccine Safety Weekly Report #39 was published 31/12/2021. Menstrual disorder is cited in the list of Medsafe's investigations into possible safety signals. The outcome of the investigation is to continue to

	monitor. The report provides a link to a Monitoring communication.[TRIM D22-5034316] On 17/11/2011, MedSafe published the Monitoring Communication [TRIM D22-5034374] ***Menstrual disorders and unexpected vaginal bleeding – Comirnaty (Pfizer COVID-19 vaccine)*** *Monitoring ongoing.* *Medsafe has been investigating a potential link between vaccination with Comirnaty and menstrual disorders or unexpected vaginal bleeding. As a result of our review we can reassure healthcare professionals and members of the public that no link has been found with vaccination.* *The Centre for Adverse Reactions Monitoring (CARM) has received a number of reports of menstrual disorders or unexpected vaginal bleeding following vaccination with Comirnaty. Medsafe conducted a full review of the cases, as well as the international published literature, and post-marketing safety reports provided by the Sponsor (Pfizer).* ***No evidence was found to suggest a link between vaccination with Comirnaty and menstrual disorders****.* ***Additional information*** *Cases reported to CARM up to 7 October 2021 include 503 reports of heavy menstrual periods, early or unexpected menstrual periods, breakthrough bleeding, late or delayed menstrual periods, painful menstrual periods, and post-menopausal bleeding, in line with reporting seen in other countries. These case numbers are low when considering how commonly menstrual disorders normally occur, and the number of vaccines that have been administered.* *Pfizer recently conducted an in-depth analysis of post-marketing safety data and found no safety signal for heavy menstrual bleeding or post-menopausal bleeding. Several international medicines regulatory bodies, including the Medicines and Healthcare products Regulatory Agency (MHRA, United Kingdom), the European Medicines Agency (EMA, European Union), and the Therapeutic Goods Administration (TGA, Australia) also conducted investigations and found no link between menstrual disorders or unexpected vaginal bleeding and Comirnaty vaccination. Similarly, in New Zealand, our review found no link.* *Menstrual disorders and unexpected vaginal bleeding occur commonly in the population, irrespective of vaccination, and there are many possible underlying causes, including anxiety caused by the ongoing pandemic. Any changes occurring after COVID-19 vaccination are likely to be temporary, with no evidence that these temporary changes will impact future fertility.* *Information about Comirnaty, including known side effects, can be found in the consumer medicine information (CMI) and data sheet.* ***Regulator actions*** *This issue was discussed with the COVID-19 Vaccine Independent Safety Monitoring Board (CV-ISMB) on 27 October 2021, who recommended Medsafe communicate their agreement with the conclusion that there is no evidence to support a link between menstrual disorders and Comirnaty administration.* *Medsafe will continue to monitor the rate and pattern of occurrence of this issue.*
Other international regulators (via ICMRA PV Network and ACCESS)	ICMRA meeting 16 November 2021 - MHRA informed the meeting that *A small retrospective study of menstrual changes after COVID-19 vaccines, which has gone up as a pre-print on 15 Nov*: *https://www.medrxiv.org/content/10.1101/2021.11.15.21266317v1* *-3 November 2021: https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions* [TRIM D21-3337101] **NOTE** - Pre-print article reviewed in Literature section of TIP.

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	Review of the following international meeting notes/ minutes did not find any mention of Menstrual disorders: • Committee for Medicinal Products for Human Use (CHMP) meeting 25 November 2021 [TRIM D21-3373702] • EMA Pandemic Taskforce COVID-ETF meeting 18 November 2021 [TRIM D21-3347990]

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Literature	1. Male V. Menstrual changes after covid-19 vaccination BMJ 2021; 374 :n2211 doi:10.1136/bmj.n2211 https://www.bmj.com/content/374/bmj.n2211 [TRIM D22-5026204] Changes to periods and unexpected vaginal bleeding are not listed in the current product information for COVID-19 vaccines, but primary care clinicians and those working in reproductive health are increasingly approached by people who have experienced these events shortly after vaccination. Most people who report a change to their period after vaccination find that it returns to normal the following cycle and, importantly, there is no evidence that covid-19 vaccination adversely affects fertility. In clinical trials, unintended pregnancies occurred at similar rates in vaccinated and unvaccinated groups. In assisted reproduction clinics, fertility measures and pregnancy rates are similar in vaccinated and unvaccinated patients. Menstrual changes have been reported after both mRNA and adenovirus vectored covid-19 vaccines, suggesting that, if there is a connection, it is likely to be a result of the immune response to vaccination rather than a specific vaccine component. Vaccination against human papillomavirus (HPV) has also been associated with menstrual changes. Indeed, the menstrual cycle can be affected by immune activation in response to various stimuli, including viral infection: in one study of menstruating women, around a quarter of those infected with SARS-CoV-2 experienced menstrual disruption. Biologically plausible mechanisms linking immune stimulation with menstrual changes include immunological influences on the hormones driving the menstrual cycle or effects mediated by immune cells in the lining of the uterus, which are involved in the cyclical build-up and breakdown of this tissue. Research exploring a possible association between covid-19 vaccines and menstrual changes may also help understand the mechanism. Although reported changes to the menstrual cycle after vaccination are short lived, robust research into this possible adverse reaction remains critical to the overall success of the vaccination programme.

Vaccine hesitancy among young women is largely driven by false claims that covid-19 vaccines could harm their chances of future pregnancy. Failing to thoroughly investigate reports of menstrual changes after vaccination is likely to fuel these fears.
If a link between vaccination and menstrual changes is confirmed, this information will allow people to plan for potentially altered cycles.
Clear and trusted information is particularly important for those who rely on being able to predict their menstrual cycles to either achieve or avoid pregnancy.

2. Edelman, A, Boniface, E, Benhar, E, Han, L, Matteson, K, Favaro, Pearson, C, Darney, B. Association between Menstrual cycle length and Coronavirus disease 2019 (COVID-19) Vaccination, Obstetrics & Gynecology 2022; VOL. 00, NO. 00, MONTH 2022 [TRIM D22-5026387]

The study described in this article is considering potential changes in menstrual cycle length following COVID-19 vaccination.
The authors acknowledge that concerns about a possible association between coronavirus disease 2019 (COVID-19) vaccination and abnormal menstrual cycles may lead to vaccine hesitancy. They note that clinical trials of the current COVID-19 vaccines did not collect menstrual cycle outcomes postvaccine and that the lack of evidence limits the ability to address these concerns and to provide advice to individuals who menstruate about what to expect.
The authors Edelman et al, acknowledge that menstrual cyclicity is an overt sign of health and fertility. Menstrual characteristics are not static, with variability exists month to month across an individual's lifespan.
The study was a retrospective cohort analysis of menstrual cycle data that was collected prospectively. The cycle data ranged from October 2020 to September 2021, with initial doses administered between December 202o and July 2021. The vaccines included in the study were PF, Janssen and Spikevax. 23,754 menstrual cycles prospectively reported by 3.959 individuals were evaluated to eastablish whether the vaccine is associated with menstrual cycle disturbances during cycles when vaccination occurs. After adjusting for confounders, they found that normally cycling individuals experienced small variations in cycle length regardless of vaccination status.

Statistically significant differences existed between vaccination status groups, but the change in cycle length was less than 1 day, which is below the reportable difference in the menstrual cycle tracking application and is not clinically significant. A subset of individuals who received both vaccine doses in a single cycle had, on average, an adjusted 2-day increase in their vaccination cycle length compared with unvaccinated individuals. Although approximately 10% of these individuals experienced a clinically notable change in cycle length of 8 days or more, this change attenuated quickly within two postvaccine cycles. They found no change in menses length between or within vaccination cohorts.
The authors concluded that their findings are re-assuring as they found no population-level clinically meaningful change in menstrual cycle length associated with COVID-19 vaccination. Individuals receiving two COVID-19 vaccine doses in a single cycle do appear to experience a longer but temporary cycle length change.
Coronavirus disease 2019 (COVID- 19) vaccination is not associated with changes in menses length.
The authors add that additional research is needed to determine how COVID-19 vaccination could potentially influence other menstrual characteristics, such as associated symptoms (pain, mood changes, etc.) and characteristics of bleeding (including heaviness of flow).

3. Norwegian Institute of Public Health
https://www.fhi.no/en/studies/ungvoksen/increased-incidence-of-menstrual-changes-among-young-women/ [TRIM: D22-5026156]

On 21/12/2021, the Norwegian Institute of Public Health published the initial results from their major study of the association between COVID-19 vaccines and menstrual changes. These results are based on data collected from 6,000 women aged 18–30 years who are participating by answering questions about their periods and any menstrual changes via online questionnaires in the UngVoksen (Young Adult) cohort study in the period 21 October to 11 November 2021. **The study has not yet been peer-reviewed but has been submitted for preprint.** Results from the first study:

- There was a high incidence of the various menstrual changes* among menstruating women aged 18–30 years. As many as 37.8 per cent reported at least one of the changes during their last period before vaccination.
- After the first dose, 39.4 per cent reported at least one change, and after the second dose, 40.9 per cent.
- In total, 7.6 per cent of participants reported that their last period before vaccination with the first dose was heavier than normal. After vaccination, almost twice as many, 13.6 per cent, reported that the first period after the vaccine was heavier than normal. The same pattern is seen for prolonged bleeding, for shorter intervals between menstrual cycles and for more painful periods than normal.
- There was no difference before and after vaccination in the incidence of prolonged intervals between menstrual cycles, breakthrough bleeding or period-like pains without bleeding after the first dose.
- After the second dose, the incidence of various disturbances increased.
- Menstrual changes after the first dose were short-lived and returned to normal by the time for vaccination with the second dose, approximately two to three months after vaccination with the first dose.
- Among women who reported menstrual changes after the first dose, 92.3 per cent were also vaccinated with dose 2. Among women who did not report any disturbances after the first dose, 94 per cent were vaccinated with dose 2.
- Among women who experienced changes after the first dose, almost two out of three women also experienced them after the second dose.
- Data about the duration of menstrual changes after dose 2 are not yet available, but this will continue to be monitored.

*Changes studies among participants were the incidence of:

- Heavier periods than normal
- Longer bleeding duration than normal
- Shorter interval between periods than normal
- Longer interval between periods than normal
- Unexpected breakthrough bleeding
- More painful periods than normal
- Period-like pains without bleeding

4. Alvergne A, Kountourides G, Argentieri M, Agyen L, Rogers N, Knight D, Sharp G, Maybin J, Olszewska Z. COVID-19 vaccination and menstrual cycle changes: A United Kingdom (UK) retrospective case-control study. **Preprint and not peer-reviewed paper COVID-19 vaccination and menstrual cycle changes: A United Kingdom (UK) retrospective case-control study | medRxiv** [TRIM D22-5036874]

The authors acknowledge that has been increasing public concern that COVID-19 vaccines cause menstrual cycle disturbances, yet there is currently limited data to evaluate the impact of vaccination on menstrual health. The study objectives were

	to evaluate the prevalence of menstrual changes following vaccination, to test potential risk factors for any such changes and to identify patterns of symptoms in participant's written accounts. They performed a secondary analysis of a retrospective online survey conducted in March 2021 in the UK before there had been widespread media regarding potential impacts of COVID-19 vaccination on menstruation. 4,989 participants who were pre-menopausal and vaccinated were selected for this analysis. ***Findings*** 80% of participants did not report any menstrual cycle changes up to 4 months after their first COVID-19 vaccine injection. Current use of combined oral contraceptives was associated with lower odds of reporting any changes by 48%. Odds of reporting any menstrual changes were increased by 44% for current smokers and by more than 50% for individuals with a positive COVID status (acute COVID or long COVID). ***Conclusions*** Following vaccination for COVID-19, menstrual disturbance occurred in 20% of individuals in a UK sample. Out of 33 variables investigated, smoking and a previous history of SARS-CoV-2 infection were found to be risk factors while using oestradiol-containing contraceptives was found to be a protective factor. Diverse experiences were reported, from menstrual bleeding cessation to heavy menstrual bleeding. 5. Lee K, Junkins E, Urooba F, Cox M, Clancy K. Charaterizing menstrual bleeding changes occurring after SARS-CoV-2 vaccination. **Preprint and not peer-reviewed paper** [TRIM The authors contend that many people began sharing that they experienced unexpected menstrual bleeding after SARS-CoV-2 inoculation and that this emerging phenomenon was understudied. They investigated menstrual bleeding patterns among currently and formerly menstruating people, with a research design based off their expectations that these bleeding changes related to changes in clotting or inflammation, affecting normal menstrual repair. In this sample (35,572 woman-only identifying and 3,557 gender diverse), 42% of people with 36 regular menstrual cycles bled more heavily than usual, while 44% reported no change, after being vaccinated. Among people who typically do not menstruate, 71% of people on long-acting reversible contraceptives, 39% of people on gender-affirming hormones, and 66% of post-menopausal people reported breakthrough bleeding. They found increased/breakthrough bleeding was significantly associated with age, other vaccine side effects (fever, fatigue), history of pregnancy or birth, and ethnicity. The authors conclude that while these report changes to menstrual bleeding are not uncommon nor dangerous, attention to these experiences is necessary to build trust in medicine.
Biological plausibility	Biologically plausible mechanisms linking immune stimulation with menstrual changes include immunological influences on the hormones driving the menstrual cycle or effects mediated by immune cells in the lining of the uterus, which are involved in the cyclical build-up and breakdown of this tissue. • Male V. Menstrual changes after covid-19 vaccination BMJ 2021; 374 :n2211 doi:10.1136/bmj.n2211 https://www.bmj.com/content/374/bmj.n2211 TRIM [D22-5026204]

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6. Conclusion

Conclusion	This is the second review of Menstrual disorders following COVID019 vaccination. This earlier review conducted in August 2021 recommended continued routine monitoring. [TRIM D21-2947788] Several of the MedDRA Preferred Terms for Menstrual disorders flagged in September to October 2021 DPAR for PF and Postmenopausal Haemorrhage flagged for AZ. The reporting rate of all menstrual disorders for PF and Spikevax is approximately double that of AZ for women of all ages.

	The AZ sponsor's bimonthly MSSR – 01/08/2021 to 30/09/2021 included a review of post-menopausal haemorrhage. The review concluded that there is no evidence currently to conclude that the reported cases of Post-menopausal Haemorrhage, can be causality related to AZ and that their earlier conclusion of no evidence that the reported cases of menstrual disorders could be causality related to AZ remains. The PF sponsor's PSUR – 19/12/2021 to 18/06/2021 included a review of menstrual disorders which concluded that the sponsor analysis did not support a causal association between vaccination and menstrual alteration in women. The MHRA reports that following their rigorous evaluation completed to date, a link between changes to menstrual periods and related symptoms and COVID-19 vaccines has not been identified. The MHRA reports that the number of reports of menstrual disorders and vaginal bleeding is low in relation to both the number of people who have received COVID-19 vaccines to date and how common menstrual disorders are generally. The menstrual changes reported are mostly transient in nature and there is no evidence to suggest that COVID-19 vaccines will affect fertility. The literature provides early evidence that the menstrual changes associated with COVID-19 vaccination are temporary and reversible and do not impact long term fertility. However, it is acknowledged that concerns about a possible association between COVID-19 vaccination and abnormal menstrual cycles may lead to vaccine hesitancy and that more research is required to provide evidence to address these concerns and to provide advice to individuals who menstruate about what to expect. Based on these conclusions, that the menstrual changes are transient and not clinically significant, it is the recommendation of this review to continue routine monitoring. The provision of clear Public health information about the transient and reversible nature of the menstrual changes following COVID-19 vaccination may be helpful in addressing women's concerns and assisting health professionals to provide advice about what to expect.
Proposed action	☐**Refer to Stream B – MAVIS Evaluation Stream** ☐**Refer to Stream C – Regulatory Outcomes Stream (ROS)** ☐**Refer to <Other>** *(delete '<Other>', and specify which area, e.g. VERA)* ☒**Routine monitoring**

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Direct workflow referral template: vSTRS to ROS

Disclaimer: This template is to be used for referrals from vaccine-STRS (vSTRS) to the Regulatory Outcomes Stream (ROS) that have not involved creation of a Targeted Investigation Process (TIP). This may include an adverse event identified from a vaccine DPAR or via a notification from an international regulator, which is then referred directly to ROS for inclusion in a vaccine PI.

TRIM: D22-6166179

mRNA COVID-19 vaccines (Comirnaty & Spikevax) and heavy menstrual bleeding	
Product details	Comirnaty (tozinameran); Comirnaty Original/Omicron BA.1 (tozinameran and rilozinameran; Spikevax (elasomeran); Spikevax Bivalent Original/Omicron (elasomeran/imelasomeran)
Signal source	The TGA via the Regulatory Outcomes Stream (ROS) was informed that the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) have requested the inclusion of heavy menstrual bleeding (frequency unknown) including the statement: 'Most cases appear to be non-serious and temporary in nature'. The update will be included in *In Section 4.8 Undesirable effects, Table1: Adverse reactions from clinical trials and post-authorisation experience in individuals* in both the Comirnaty and Spikevax European product information (PI). This update will be included in the SmPC, the package leaflet and labelling. 21/11/2022: ROS requested this review to inform their decision about whether to request similar updates to the Australian PIs. [TRIM D22-6166500] <u>Previous investigations conducted by the TGA</u> The TGA has conducted two Targeted Investigative Reviews (TIPs) of Menstrual disorders associated with COVID-19 vaccination, neither of which resulted in PI updates and the issue was returned to routine pharmacovigilance monitoring following both TIPs. The first TIP was conducted in August 2021 and resulted in the publication of an article in the weekly COVID-19 vaccine weekly safety report on the TGA website. [TRIM: D21-2947788] The second TIP was conducted in January 2022. [TRIM: D22-5024968]
Australian case numbers	<u>Comirnaty</u> Search of the TGA's Adverse Event Management System (AEMS) Date: 23/11/2022 QLIK COVID-19 Vaccine Surveillance Platform Drug: Comirnaty Sex: female The search identified 52,882 reports of adverse events associated with Comirnaty reported by females. The above search was repeated with the addition of the preferred term (PT) 'heavy menstrual bleeding'. This search identified 853 reports of heavy menstrual bleeding. Heavy menstrual bleeding is the 41st most reported reaction term by females (approximately 2% of all reports of adverse events associated with Comirnaty reported by females). Of note, the search identified that menstrual disorder

is the 22nd most reported reaction term by females (approximately 4% of all reports of adverse events associated with Comirnaty reported by females).

The Qlik searches were repeated with the addition of the age filter 50 years and under, to capture most women prior to menopause. Cancer Australia reports that the average age of menopause in Australia is 51 years (2022).

The search for all reports from females 50 years and under identified a total of 38,973 reports.

Of these 38,973 reports, 2% (737 reports) are reports of heavy menstrual bleeding. Heavy menstrual bleeding is the 35th most reported reaction term in females 50 years and under. Of note, menstrual disorder is the 19th most reported reaction term in the same cohort accounting for approximately 5% (1,802 reports) of reports.

The following analysis was conducted on the 737 reports of heavy menstrual bleeding in females aged 50 years and under. The PCDs are filed in TRIM: D22-6166520 D22-6166529 D22-6166540

Of the 737 reports 440 reports are for 2021 and 297 are for 2022.

Age range reported

Of the 737 reports:

- 3.66% (27 reports) are reported in the 12–19-year age group
- 18% (133 reports) are reported in the 20-29-year age group
- 42% (311 reports) in the 30-39-year age group
- 34% (251 reports) in the 40-49-year age group and
- 2% (15 reports) were for females aged 50 years.

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Management of the event

- Approximately 15% (110 reports) reported they were managed by a GP assessment
- 1% (7 reports) reported using a Helpline
- 2% (16 reports) reported management by Hospital admission
- 7% (48 reports) reported management by the Hospital emergency department
- 1% (7 reports) reported their management as ‘none’. None in 7 reports
- 1% (7 reports) reported management by a Nurse assessment
- 15% (108 reports) reported management as ‘self’

The majority of reports 60% (444 reports) do not provide the management of the event information.

Reaction outcome

No fatal outcomes are reported.

- 24% (176 reports) reported the outcome as ‘not recovered/not resolved /ongoing’

- 8% (57 reports) reported the outcome as 'Recovered/resolved'
- 0.1% (1 report) reported the outcome as 'recovered/resolved with sequelae'
- 3% (23 reports) reported the outcome as recovering/resolving

The majority of reports 65% (480 reports) did not include the outcome information.

Reporter

- 5% (35 reports) were reported by a health professional
- 61% (452 reports) were reported by patient / consumer
- 0.5% (4 reports) were reported by sponsor
- 33.5% (246 reports) reported by state or territory health department

Reports by dose number

Of the 737 reports

- 39% (291 reports) of reports are associated with dose one
- 35% (261 reports) of reports are associated with dose two
- 8% (58 reports) of reports are associated with dose three
- 0.1% (One report) of reports is associated with dose four.

Dosage information was not provided in the remaining 17% (126 reports) of reports.

Time to onset (TTO)

Due to the large number of reports and the difficulties determining the TTO in QLIK, the TTO has been calculated as indicative using the information in the 30 most recent reports of heavy menstrual bleeding submitted to the TGA's AEMS. [TRIM D22-6166555]

Of the 30 reports selected, 47% (14 reports) do not include the TTO.

Of the remaining 16 reports, the TTO ranges from 0 (the date of vaccination) to 255 days following vaccination. The median TTO is three days, noting that 10 of the 16 reports (63%) had a TTO of 7 days or less. The mean TTO is 32 days (this is skewed by the large outliers such as the report with a TTO of 225 days).

Spikevax

Search of the TGA's Adverse Event Management System (AEMS)

Date: 23/11/2022

QLIK COVID-19 Vaccine Surveillance Platform

Drugs: Spikevax and Spikevax Bivalent Original/Omicron

Sex: female

The search identified 4,771 reports of adverse events associated with Spikevax that were reported by females. Of these 37 were reported in association with Spikevax Bivalent Original/Omicron

The above search was repeated with the addition of the preferred term (PT) 'heavy menstrual bleeding'.

This search identified 97 reports of heavy menstrual bleeding. Heavy menstrual bleeding is the 40th most reported reaction term by females (approximately 2% of all reports of adverse events associated with Spikevax reported by females). Of note, menstrual disorder is the 21st most reported

reaction term by females (approximately 5% of all reports of adverse events associated with Spikevax reported by females).

The Qlik searches was repeated with the addition of the age filter 50 years and under.

The search for all reports from females 50 years and under identified a total of 3,119 reports.

Of these 3,119 reports, 3% (88 reports) are reports of heavy menstrual bleeding. Heavy menstrual bleeding is the 35th most reported reaction term in females 50 years and under. Of note, menstrual disorder is the 18th most reported reaction term in the same cohort accounting for approximately 6% (198 reports) of reports.

The following analysis was conducted on the 88 reports of heavy menstrual bleeding in females aged 50 years and under. The PCDs are filed in TRIM: D22-6166569

Of the 88 reports 36 reports are for 2021 and 52 are for 2022.

Age range reported

Of the 88 reports:

- 6% (5 reports) are reported in the 12–19-year age group
- 24% (21 reports) are reported in the 20-29-year age group
- 42% (37 reports) in the 30-39-year age group
- 27% (24 reports) in the 40-49-year age group
- 1% (1 report) was aged 50 years.

s22 [redacted]

Management of the event

- Approximately 9% (8 reports) reported they were managed by GP assessment
- 1% (1 report) reported management by Hospital admission
- 7% (6 reports) reported management by the Hospital emergency department
- 2% (2 reports) reported their management as 'none'.
- 1% (1 report) reported management by a Nurse assessment
- 19% (17 reports) reported management as 'self'

The majority of reports 61% (54 reports) do not provide the management of the event information.

Reaction outcome

No fatal outcomes are reported.

- 66% (58 reports) reported the outcome as 'not recovered/not resolved /ongoing'
- 12.5% (11reports) reported the outcome as 'Recovered/resolved'
- 7% (6 reports) reported the outcome as recovering/resolving

The remaining 15% of reports (13 reports) did not include the outcome information.

Reporter

- 6% (5 reports) were reported by a health professional
- 65% (57 reports) were reported by patient / consumer
- 30% (26 reports) reported by state or territory health department

Reports by dose number

Of the 88 reports

- 39% (34 reports) of reports are associated with dose one
- 31% (27 reports) of reports are associated with dose two
- 9% (8 reports) of reports are associated with dose three

Dosage information was not provided in 22% of reports (19 reports).

Time to onset (TTO)

TTO has been reviewed for all 88 reports. [TRIM D22-6166582]
Of the 88 reports selected, 49% (43 reports) do not include the TTO.
Of the remaining 45 reports, the TTO ranges from 0 days (the date of vaccination) to 50 days following vaccination.

- 32 reports have the TTO between 0-7 days
- 6 reports have the TTO between 8-14 days
- 2 reports have the TTO between 15-21 days.
- 4 reports have the TTO between 22-35 days
- 1 report has the TTO as 50 days.

The median TTO is 2 days, noting that 32 of 88 reports (71%) have a TTO of 0-7 days. The mean TTO is seven days.

Quantitative evidence

DPAR

Comirnaty and the PT 'heavy menstrual bleeding' flagged on the July to August 2022 Disproportionality Analysis Report (DPAR) on the data in the TGA AEMS. The other COVID-19 vaccines did not flag for this signal on this DPAR.

July-August 2022 DPAR [TRIM D22-5890555]			
PRR	PRR LCI	IC	IC_{025}
5.13	4.47	0.97	0.86
Based on 10 cases in period. 849 cases in total			

Comirnaty and 'heavy menstrual bleeding' also flagged on the May to June 2022 DPAR. The other COVID-19 vaccines did not flag for this signal on this DPAR.

May-June 2022 DPAR [TRIM D22-5830538]			
PRR	PRR LCI	IC	IC_{025}
5.23	4.55	0.99	0.87
Based on 49 cases in period. 836 cases in total			

Reporting Rates

Table: Overall reporting rate for heavy menstrual bleeding in females

Vaccine name	Dose numbers	Observed cases	Reporting rate per 100,000 doses
Comirnaty	23,052,435	853	3.7
Vaxzevria	6,839,448	142	2.08
Spikevax	2,762,580	96	3.48
Nuvaxovid	127,154	13	10.22

The highest reporting rate of heavy menstrual bleeding for all females was detected in association with Nuvaxovid.
Comirnaty has a slightly higher reporting rate that Spikevax. Both the mRNA vaccines have higher reporting rates than Vaxzevria.

Table: Reporting rate of heavy menstrual bleeding in females 50 years and under

Vaccine name	Dose numbers	Observed cases	Reporting rate per 100,000 doses
Comirnaty	15,492,588	737	4.76
Vaxzevria	1,136,026	114	10.03
Spikevax	1,393,016	87	6.25
Nuvaxovid	68,985	9	13.04

The highest reporting rate of heavy menstrual bleeding in females '50 years and under' was detected in association with Nuvaxovid.
The reporting rate of heavy menstrual bleeding in females '50 years and under' for Vaxzevria is just over twice that for Comirnaty and approximately 1.6 times higher than Spikevax.

Table: Reporting rate of heavy menstrual bleeding in females over 50 years

Vaccine name	Dose numbers	Observed cases	Reporting rate per 100,000 doses
Comirnaty	7559847	41	0.54
Vaxzevria	5703422	20	0.35
Spikevax	1369564	1	0.07
Nuvaxovid	58169	1	1.72

The reporting rate is approximately 1.5 times higher for Comirnaty than Vaxzevria but low across both vaccines. As expected, the reporting rates for all vaccines are higher in the 50 years and under age group than the over 50 age group.

Data Sources for the Reporting Rate Calculations
Australian Immunisation Register COVID-19 vaccine dose data to 13/11/2022 prepared by the Technical Safety and Improvement Section (TSIS) [TRIM D22-6166590]
Total number of doses by COVID-19 vaccines all females
Vaxzevria 6,839,448
Comirnaty 23,052,435
Spikevax 2,762,580

	Nuvaxovid 127,154 <u>Total number of doses by COVID-19 vaccines all females 50 years and under</u> Vaxzevria 1,136,026 Comirnaty 15,492,588 Spikevax 1,393,016 Nuvaxovid 68,985 <u>Total number of doses by COVID-19 vaccines all females over 50 years</u> Vaxzevria 5703422 Comirnaty 7559847 Spikevax 1369564 Nuvaxovid 58169 QLIK search of AEMS for reports received up to 13/11/2022 Search Date: 21/11/2022 Default bookmark applied Sex: female Trade Name: COVID-19 vaccines Reaction term: heavy menstrual bleeding. Total number of reports: 1101 [TRIM D22-6166599] Comirnaty 853 Vaxzevria 142 Spikevax 96 Nuvaxovid 13 COVID-19 vaccine (Trade name unknown) 5. Age filter '50 years and under' applied to QLIK search [TRIM D22-6166605] Total number of reports 946 Comirnaty 737 Vaxzevria 114 Spikevax 87 Nuvaxovid 9 COVID-19 vaccine (Trade name unknown) 5 Age filter 'over 50 years' applied to QLIK search [TRIM D22-6166610] Total number of reports 61 Comirnaty 41 Vaxzevria 20 Nuvaxovid 1 Spikevax 1
s33	[redacted]

s33

[redacted]

Literature	PubMed search Date: 24/11/2022 Search terms: Heavy menstrual bleeding and COVID-19 vaccines The search identified seven articles. [TRIM D22-6168591] Overall, the evidence in the literature is not compelling and does not provide strong evidence to support this signal. However, additional information obtained from the EMA PRAC contained stronger evidence. This is presented in the *European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) Signal assessment* section below. The literature does present evidence of the temporal association of transient changes to the length of the menstrual cycle following COVID-19 vaccination but not of heavy menstrual bleeding following COVID-19 vaccination. Of the seven articles, one is a literature review on studies reporting menstrual abnormalities after COVOD-19 vaccination:

Nazir M et al[1] (2022) conducted a systematic literature review on studies reporting any menstrual abnormalities after the COVID-19 vaccine. A total of 78 138 vaccinated females were included in this review from 14 observational studies (3 cohort and 11 cross-sectional). 12 of the 14 studies were from developed countries (Saudi Arabia, USA, Norway, UK, and Italy) and two studies were conducted in less developed countries in East Africa. Due to the lack of published research articles, preprints were also included in this review. The authors report that 39 759 women (52.05% of the total) had some form of a menstrual problem after vaccination. However, the review reported heterogeneity in the occurrence of menstrual abnormalities following vaccination. Menorrhagia, metrorrhagia, and polymenorrhea were the most commonly observed problems and the overall study-level rate of menstrual abnormality ranged from 0.83% to 90.9%. Most of the cross-sectional studies considered in this review were unable to report a causal relationship between menstrual irregularities and COVID-19 vaccination status. [TRIM D22-6168685]

Edelman et al[2] (2022) conducted a global retrospective cohort study of prospectively collected data to identify whether COVID-19 vaccinations are associated with menstrual changes. The 19,622 participants used the menstrual cycle tracking app Natural Cycles. Participants were aged 18-45 years with cycle lengths of 24-38 days and consecutive data for at least three cycles before and one cycle after COVID-19 vaccination (vaccinated group n=14,936) and those with at least four consecutive cycles over a similar time period (unvaccinated group n=4686). The mean change within individuals was assessed by vaccination group for cycle and menses length (mean of three cycles before vaccination to the cycles after first and second dose of vaccine and the subsequent cycle). Mixed effects models were used to estimate the adjusted difference in change in cycle and menses length between the vaccinated and unvaccinated.

Two thirds of the vaccinated cohort received Comirnaty, 17.46% received Spikevax, 9.06% received Vaxzevria, and 1.89% Janssen.
Individuals who were vaccinated had a less than one day adjusted increase in the length of their first and second vaccine cycles, compared with individuals who were not vaccinated. The adjusted difference was larger in people who received two doses in a cycle. One cycle after vaccination, cycle length was similar to before the vaccine in individuals who received one dose per cycle, but not yet for individuals who received two doses per cycle compared with unvaccinated individuals. Changes in cycle length did not differ by the vaccine's mechanism of action (mRNA, adenovirus vector, or inactivated virus). Menses length was unaffected by vaccination. The authors conclude

[1] Nazir M, Asghar S, Rathore MA, Shahzad A, Shahid A, Ashraf Khan A, Malik A, Fakhar T, Kausar H, Malik J. Menstrual abnormalities after COVID-19 vaccines: A systematic review. Vacunas. 2022 Sep-Dec;23:S77-S87. doi: 10.1016/j.vacun.2022.07.001. Epub 2022 Jul 19. PMID: 35873308; PMCID: PMC9294036. [TRIM D22-6168685]

[2] Edelman A, Boniface ER, Male V, Cameron ST, Benhar E, Han L, Matteson KA, Van Lamsweerde A, Pearson JT, Darney BG. Association between menstrual cycle length and covid-19 vaccination: global, retrospective cohort study of prospectively collected data. BMJ Med. 2022;1(1):e000297. doi: 10.1136/bmjmed-2022-000297. Epub 2022 Sep 27. PMID: 36381261; PMCID: PMC9665108. [TRIM D22-6168978]

	that Covid-19 vaccination is associated with a small and likely to be temporary change in menstrual cycle length but no change in menses length. [TRIM D22-6168978]
International PI	Heavy menstrual bleeding is not currently listed in international PIs for Comirnaty and Spikevax. The EU's PI for both vaccines will be updated as discussed in this review.
ICMRA COVID-19 vaccines PV Network	22/11/2022 Meeting #36 of the International Coalition of Medicines Regulatory Authorities COVID-19 Pharmacovigilance Network. Evaluator's Meeting Notes [TRIM D22-6166626] Agenda item 2: mRNA vaccines and heavy menstrual bleeding (EMA) The EMA informed the meeting that the EMA's PRAC requested an update to the product information for both Comirnaty and Spikevax (as described above) at the 24-27 October meeting. The meeting highlights are published: https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-24-27-october-2022 The Draft PI updates from the sponsors are due to the EMA on 25/11/2022. The EMA PRAC plan to publish their report evaluation at a date yet to be determined. Other regulators including HSA, Aust, MHRA and HC informed the meeting that they plan to review their own evidence and will review the EMA PRAC report when it is published.
Sponsor assessment	Comirnaty Sponsor response: Pfizer is still in contact with the EMA on the signal. Although the company position is that we cannot conclude a causal relationship between Comirnaty and heavy menstrual bleeding, Pfizer has agreed to update the EU SmPC as shown below. **Summary of Product Characteristics** **Section 4.8 Undesirable effects** System Organ Class: Reproductive system and breast disorders [Frequency] Not known: Heavy menstrual bleeding* [Under table] * Most cases appeared to be non-serious and temporary in nature. **Package leaflet:** **Section 4 - Possible side effects** Not known (cannot be estimated from the available data): Heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature) There are no plans at this stage to update company core data sheet (CCDS) with the changes. TGA assessment: Unable to comment on this response. See conclusion below. Spikevax Spikevax response: [TRIM D22-6169176] Summary of response and TGA comment:

The sponsor has comprehensively evaluated the risk of heavy menstrual bleeding (HMB) post-vaccination with SPIKEVAX using information from the clinical trial database, company global safety database, external safety databases as well as published literature. Their evaluation concludes that there is insufficient information to establish a causal relationship between the administration of SPIKEVAX and HMB. The Sponsor's conclusion about a causal relationship is justified based on the current evidence. However, a temporal relationship has been detected in the Australian data as evidenced by the average reported time to onset of seven days.

Detailed response and TGA comments:
The sponsor explains that the rationale for this conclusion is as follows:

1. Menstrual cycles have a complex physiology and as such normal variations in these over a woman's lifespan are common.

TGA comment: The Sponsor is correct that normal variations in menstrual cycles are considered common and in the majority of cases are not necessarily clinically significant. For younger women of childbearing years this may also raise concerns about the potential for future fertility issues. Variations in an individual's usual or regular menstrual cycle, even if these are not considered clinically (medically) significant, can cause unnecessary anxiety and stress.

2. The features of a menstrual cycle (e.g. bleeding volume, pain and PMS symptoms) cannot be quantified in a standardised manner and are subjective in reporting. Most of the reporting comprises of patients' self-reports, in which introduction of multiple biases and inaccuracy are inherent limitations.

TGA comment: Heavy menstrual bleeding can be quantified by the consumer particularly if the bleeding impacts on the consumers daily life. i.e Bleeding not contained within a pad or tampon, change a pad or tampon more frequently than normal, the presence of clots, bleeding for more than 7-8 days. The high number of reports submitted by consumers for this adverse event is not unexpected. However, a transient episode of heavy menstrual bleeding while stressful for the consumer is not necessarily clinically significant. If the heavy menstrual bleeding is indeed transient and self corrects in the next cycle, intervention from a health care provider would often not be sought. The higher reporting of this AE by consumers demonstrates the high engagement of females in this issue.

3. Biological mechanisms demonstrating causal association are hypothetical, lacking definitive evidence till date. Some of these mechanisms include the presence of ACE-2 receptions on the ovaries and endometrium that could affect hormone production or endometrial response, endometrial inflammatory response mediated by immune cells in the lining of the uterus as well as alterations in coagulation system.

TGA comment: There are several plausible biological mechanisms for the development of heavy menstrual bleeding in the literature. As the sponsor has stated these have not been proven yet. However, given they are theoretically possible they should not be disregarded. Significantly, changes

	to the menstrual cycle have also been reported following infection with COVID-19 and in people affected by long-COVID. 4. Presence of multiple confounding factors for menstrual disorders e.g. stress, extreme exercise, eating disorders, obesity, and infection. TGA comment: There are many confounding factors associated with the development of heavy menstrual bleeding. However, the reports submitted by consumers are responding to a change in their 'normal' bleeding which is temporally related to vaccination. 5. Published data is unable to determine frequency and association of SPIKEVAX and HMB. TGA comment: More longitudinal studies are required to provide further information on rates and frequency. Hover, the Australian reporting rate of heavy menstrual bleeding temporally associated with Spikevax is 3.48 reports per 100,000 doses administered. Given that under reporting is a known limitation of spontaneous reporting systems such as the TGA's AEMS, the actual rate of heavy menstrual bleeding experienced is expected to be higher. 6. Clinical studies were not designed to collect menstrual cycle information in female participants. TGA comment: The fact that clinical trials do not collect this data is a limitation for the Sponsor to consider. 7. Presence of other confounding factors such as a concurrent medical condition or concurrent medications which provided plausible alternate explanations. TGA comment: The presence of other conditions / medications that provide an alternative explanation for heavy menstrual bleeding requires consideration. However, the temporal association, reporting rate, s33 [redacted], and the potential to further increase vaccine hesitancy should not be disregarded. Sponsor asserts that no new or emerging safety issue has been identified and the benefit-risk profile of the vaccine continues to be positive. They maintain that they respectfully disagree with EMA-PRAC's evaluation and consider that a PI update is not warranted at this time.
European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) Signal assessment	25/11/2022: The TGA through the ICMRA PV Network, has requested the EMA pre-publication report of their investigation of heavy menstrual bleeding and mRNA vaccines. The findings in this report may further strengthen our negotiations with the sponsors if required. 9/12/2022: EMA PRAC provided both the Spikevax and Comirnaty signal assessments of heavy menstrual bleeding. [TRIM D22-6221680] 13/12/2022:TGA summary of both signal assessments was completed. [TRIM D22-6227043] TGA evaluator comment: In both the Spikevax and Comirnaty assessments of the signal heavy menstrual bleeding, there was not initially agreement among EMA PRAC member states about whether the available information provided evidence of causality. However, after further consideration and discussion, the EMA PRAC put forward a good argument that there is a reasonable possibility of the association between these two mRNA vaccines and heavy menstrual bleeding being causal. For example,

	• Epidemiological studies
	  o Observational studies: the additional analysis by Trogstad et al which showed a statistically significant increased relative risk of heavy menstrual bleeding (in both Spikevax and Comirnaty recipients) following dose 1 and dose 2 in women who normally have regular cycles
	  o Placebo controlled trials showing higher rates of heavy menstrual bleeding in vaccine arm compared to control arm (in both Spikevax and Comirnaty recipients based on the information provided by the Sponsor)
	• Frequency, rechallenges and disproportionality of spontaneous reports (as well as the severity of some)
	• Biological plausibility (although not proven, plausible mechanisms are proposed, and it is noted by PRAC that there is not a proven mechanism for mRNA vaccine associated myocarditis which is listed in both section 4.4 and 4.8 of the Australian product information)
	
	The outcome of the EMA PRAC signal assessments of both Spikevax and Comirnaty and heavy menstrual bleeding that was based on the reports in the European database, national reviews, observational studies and the information provided by the Sponsors, was that EMA PRAC requested updates to Section 4.8 in the SmPC for both COVID-19 vaccines.

Conclusion	<u>Comirnaty</u> The TGA has identified a signal between Comirnaty and heavy menstrual bleeding in both the Australian s33 adverse event data. The preferred term heavy menstrual bleeding and Comirnaty has flagged as a local Australian signal on both the May-June 2022 (PRR 5.23) and July-August 2022 (PRR 5.13) Disproportionality Analysis Report (DPAR) on the data in the TGA Adverse Event Management System (AEMS). Reports of heavy menstrual bleeding accounts for 2% of all reports for females in association with Comirnaty at a reporting rate of 3.7 reports per 100,000 doses administered. The majority of the reports (61%) have been submitted by consumers which indicates a high level of engagement by females on this signal. s33 [redacted] The information provided in the EMA PRAC signal assessment further strengthens a reasonable causal relationship between Comirnaty and heavy menstrual bleeding. This PI update would enable health care providers to educate and reassure their female patients with the information that most cases appear to be non-serious and temporary in nature <u>Spikevax</u> The TGA has identified a signal between Spikevax and heavy menstrual bleeding s33 [redacted]. Although Spikevax and heavy menstrual bleeding has not flagged in the May-June 2022 and July to August 2022 DPARs, reports of heavy menstrual bleeding accounts for 2% of all AE reports for females in association with Spikevax at a reporting rate of 3.48 reports per 100,000 doses administered. The majority of the reports (65%) have been submitted by consumers which

indicates a high level of engagement by females on this signal who would benefit from a PI update informing them that the observed heavy menstrual bleeding is mainly non-serious and transient. The information provided in the EMA PRAC signal assessment further strengthens a reasonable causal relationship between Comirnaty and heavy menstrual bleeding.

Summary

Overall, this targeted assessment has found the reasonable possibility of the association between these two mRNA vaccines and heavy menstrual bleeding being causal, noting that it is a frequently reported reaction with high engagement from female consumers. A PI update would inform them and their treating health professionals that the observed heavy menstrual bleeding is mainly non-serious and transient. This information is being provided to consumers and health professionals in comparable counties in Europe, as part of the EMA's planned PI updates.

My recommendation, based on the information in this review, including the information in the EMA PRAC assessment of both Spikevax and Comirnaty and heavy menstrual bleeding is that the TGA write to both Sponsors using the wording below.

Proposed Australian PI updates

Comirnaty

Request that ROS write to the Pfizer requesting an update to the Australian Comirnaty Product Information (PI)

The TGA is requesting the inclusion of 'heavy menstrual bleeding' to the Australian Product information for Comirnaty. This information is being provided to consumers and health professionals in comparable counties in Europe, as part of the EMA's planned PI updates' as per above.

Requested update to the product information (in RED)

Section 4.8 Adverse effects (undesirable effects)

Post-marketing experience

Although the events listed in Table 5 were not observed in the clinical trials, they are considered adverse drug reactions for COMIRNATY as they were reported in the post-marketing experience. As these reactions were derived from spontaneous reports, the frequencies could not be determined and are thus considered as not known.

Table 5: Adverse reactions from COMIRNATY post marketing experience

System Organ Class	Adverse Drug Reaction
Immune system disorders	Anaphylaxis Hypersensitivity reactions (e.g. rash, pruritis, urticaria, angioedema, erythema multiforme)
Cardiac disorders	Myocarditis Pericarditis
Gastrointestinal disorders	Diarrhoea Vomiting
Musculoskeletal and connective tissue disorders	Pain in extremity (arm)

General disorders and administration site conditions	Extensive swelling of vaccinated limb
Nervous system disorders	Paraesthesia Hypoaesthesia Dizziness
Reproductive system and breast disorders	Non-sexually acquired genital ulceration Heavy menstrual bleeding*

*Most cases appear to be non-serious and temporary in nature

Spikevax

Request that ROS write to the Moderna requesting an update to the Australian Spikevax Product Information (PI)

The TGA is requesting the inclusion of 'heavy menstrual bleeding' to the Australian Product information for Spikevax. This information is being provided to consumers and health professionals in comparable counties in Europe, as part of the EMA's planned PI updates' as per above.

The requested update to the Product information is in RED

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Table 3: Adverse reactions from SPIKEVAX clinical trials and post authorisation experience in individuals 6 months of age and older

MeDRA system organ class	Frequency	Adverse reaction(s)
Blood and lymphatic system disorders	Very common	Lymphadenopathy
Immune system disorders		
Metabolism and nutrition disorders		
Psychiatric disorders		
Nervous system disorders		
Cardiac disorders		
Gastrointestinal disorders		
Skin and subcutaneous tissue disorders		
Musculoskeletal and connective tissue disorders		
General disorders and administration site conditions		
Reproductive system and breast disorders	unknown	Heavy menstrual bleeding*

*Most cases appear to be non-serious and temporary in nature

Australian Government
Department of Health

Surveillance and Targeted Review Stream (STRS) – Targeted Investigation Process (TIP) for vaccines

Medicines and Vaccines Investigation and Surveillance Section

TRIM reference:
D23-5253802

COVID-19 vaccines and menstrual irregularities

Date and Time completed	4/07/2023 2:00 PM

Summary

The terms menstrual irregularities and menstrual disorders cover a wide range of conditions, that are more appropriately covered under the term abnormal uterine bleeding (AUB), which has a clear medical definition, although the terms are often used interchangeably, including in this document. The term abnormal uterine bleeding (AUB) covers a broad range of conditions related to irregularities in menstrual cycles and refers to bleeding from the uterus that is abnormal in regularity, frequency, duration and/or quantity. It is estimated that between 3% and 30% of reproductive aged women will experience AUB, with irregularities most commonly occurring at menarche and around perimenopause.

Following the roll out of COVID-19 vaccines globally, there were numerous reports of menstrual cycle changes following vaccination through social media and also to adverse event reporting systems worldwide, with continued public and media interest in this topic.

Previous targeted investigation process (TIP) assessments on COVID-19 vaccines and menstrual disorders were undertaken in August 2001 and January 2022, with the outcome of continuing to monitor. Following the transfer of COVID-19 vaccine signal detection to the Vaccine Surveillance and Targeted Review Stream (Vaccine STRS), signals for several different MedDRA preferred terms relating to menstrual irregularities and abnormal menstruation started to flag in the disproportionality analysis report (DPAR) from May-June 2022, with most related to Comirnaty. Variations of these signal pairs have continued to flag on all subsequent DPARs. In December 2022, a mini-TIP on Spikevax and Comirnaty and Heavy Menstrual Bleeding (HMB) was undertaken in response to regulatory action by the European Medicines Agency to include HMB in the European product information (PI) documents for the mRNA vaccines, and subsequently HMB was also included in the Australian PIs for the mRNA vaccines. This also led to the decision to re-evaluate the association between other menstrual irregularities and COVID-19 vaccines.

On 22nd May 2023, a search of the Australian Adverse Events Management System (AEMS) database was conducted and identified 2,934 case reports of adverse events related to menstrual irregularities and COVID-19 vaccines. The most commonly reported preferred term (PT) was 'menstrual disorder' (n = 2707) followed by 'menstruation irregular' (n = 830) and 'intermenstrual bleeding' (n=359). Of note, over a third of reports (n=1011, 34.5%) co-reported heavy menstrual bleeding (HMB). Most reports were related to Comirnaty (n =2329, 79.3%). Of the remaining reports, 342 were related to Vaxzevria, 230 to Spikevax, 29 to Nuvaxovid, 14 to COVID-19 vaccine trade name not specified, one to Spikevax bivalent vaccine (TNS) and one to Spikevax bivalent vaccine (elasomeran/imelasomeran). Based on AEMS data, 'menstrual disorder' is the 22nd most commonly reported AEFI for Comirnaty in females in Australia (2,127 reports out of a total of 53,510 AEFI reports, 4%).

The median age of individuals was 36 years (range 8-59 years) noting that data analysis was restricted to menstruating individuals of reproductive age (aged 8-59 years) and 262 reports did not have an age provided. Due to the high number of reports of menstrual irregularities associated with COVID-19 vaccines in AEMS, a review of each individual report could not be undertaken. A targeted review of 27 reports coded as serious (serious criteria coded as life threatening) were reviewed. More than half the reports in AEMS were made by consumers (61.7%), with only a small proportion of reports made by health professionals (4.4%). Overall, the minimal level of detail, often absent time to onset information and low quality of reports provides limited support of an association. Whilst not all reports could be reviewed, it is important to note that general scanning of the reports identified several reports that described a recurrence of menstrual irregularities with subsequent doses of COVID-19 vaccine, providing evidence of positive rechallenge.

Using AEMS data the reporting rate of menstrual irregularities (combined PTs) for all COVID-19 vaccines was rare (≥ 1/10,000 to < 1/1,000). The reporting rates for Comirnaty, Vaxzevria and Spikevax were similar (12.5-14.1 per 100, 000 doses), with the reporting rate for Nuvaxovid being relatively higher (28.5 per 100, 000 doses), noting the overall number of reports associated with Nuvaxovid was low (n = 28).

The diverse range of clinical entities that fall under the term abnormal uterine bleeding, and the large number of potential underlying causes makes determining a background incidence rate difficult and as such an observed versus expected analysis was not conducted and thus no comment on whether reports following vaccination are higher than expected in the background population can be made.

With the exception of HMB in the Australian, EMA and Medicines and Healthcare Products Regulatory Agency (UK) (MHRA) PI documents for the mRNA vaccines, none of the PI documents for any COVID-19 vaccines include reference to menstrual irregularities. Interestingly, the US Centres for Disease Control (CDC) does refer to possible menstrual cycle changes on their website under frequently asked questions and the Australian Technical Advisory Group on Immunisation (ATAGI) also references a study reporting that COVID-19 vaccines may be associated with a small and temporary change in menstrual cycle length. Other regulators including the MHRA (UK) and Medsafe (New Zealand) have statements regarding menstrual irregularities and COVID-19 vaccinations expressing that the issue has been reviewed and there is currently insufficient evidence of an association, but it will continue to be monitored.

Whilst biologically plausible mechanisms for COVID-19 vaccines causing menstrual cycle changes through immunological effects on the hypothalamic-pituitary-ovarian axis have been suggested, results from the published literature provide conflicting evidence of an association. Many of the current studies are cross-sectional observational studies with several potential biases.

In summary, the high volume of reports to pharmacovigilance databases and increasing number of studies in the published literature provide a growing evidence base for a possible association between menstrual disorders (excluding HMB) and COVID-19 vaccines, however, the current evidence remains insufficient to strongly support a causal relationship. Establishing a causal relationship in this instance is challenging due to the wide number of conditions that are encapsulated by the terms abnormal uterine bleeding/menstrual irregularities and the numerous underlying causes, numerous potential confounding factors, the common occurrence of menstrual cycle abnormalities and the limitations of using adverse event reporting data, which is subject to both under-reporting and potentially stimulated reporting given the public interest and media attention on this topic. The published literature on COVID-19 vaccines and menstrual irregularities shows mixed findings and significant limitations with the majority of studies to date being observational and subject to potential biases. Assessment of Australian specific data from AEMS is limited by the generally poor quality of reports, often with very limited information and no time to onset information. The diverse range of clinical entities that fall under the term abnormal uterine bleeding, and the large number of potential underlying causes also makes determining a background incidence rate difficult and as such an observed versus expected analysis was not conducted and thus no comparison as to whether reports following vaccination are higher than expected in the background population can be made.

Of note, the majority of reports of menstrual irregularities in AEMS are associated with Comirnaty. The majority of DPAR signals related to menstrual irregularities have also been related to Comirnaty, and s33 [redacted] Whilst

there is insufficient evidence to request inclusion of menstrual irregularities in the product information document for Comirnaty at this stage, the sponsor should be requested to undertake a signal analysis for menstrual irregularities.

Finally, while the focus of this tip was to evaluate menstrual irregularities in association with COVID-19 vaccines in menstruating individuals of reproductive age, it has been noted that there were reports of vaginal haemorrhage and post-menopausal bleeding in females outside the reproductive age group in AEMS and consideration should be given to doing a separate TIP or mini-TIP to further evaluate abnormal uterine bleeding outside the reproductive age group.

Causality/public health impact

Strength of the association	There is conflicting evidence of a causal association between COVID-19 vaccines and anormal uterine bleeding/menstrual irregularities as evidenced by s33 [redacted] contradictory findings in the literature and inconclusive evidence in the Australian Adverse Event Management System (AEMS) data. s33 [redacted] The evidence in the literature is also mixed, with some studies reporting no changes to menstrual cycles following COVID-19 vaccination, whilst others have reported a higher proportion of participants experiencing changes in cycle length, spotting, polymenorrhoea and oligmenorrhoea following COVID-19 vaccination compared with unvaccinated individuals. Using AEMS data the reporting rate of menstrual irregularities (combined PTs) for all COVID-19 vaccines was rare (≥ 1/10,000 to < 1/1,000). The reporting rates for Comirnaty, Vaxzevria and Spikevax were similar (12.5- 14.1 per 100, 000 doses), with the reporting rate for Nuvaxovid being relatively higher (28.5 per 100, 000 doses), noting the overall number of reports associated with Nuvaxovid was low (n = 28). The diverse range of clinical entities covered by the terms menstrual disorders/menstrual irregularities/abnormal uterine bleeding, and the large number of potential underlying causes makes determining a background incidence rate difficult and as such an observed versus expected analysis was not undertaken.
Consistency of reporting	The European Medicine Association (EMA) and Medicines and Healthcare Products Regulatory Agency (UK) (MHRA) list Heavy Menstrual Bleeding under section 4.8 of the product information (PI) documents for Spikevax and Comirnaty and their bivalent formulations, but no reference to any other menstrual disorders. None of the other international regulators make any reference to abnormal uterine bleeding or menstrual irregularities in their PI documents, although the Centres for Disease Control (US) does refer to possible menstrual cycle changes on their website under frequently asked questions and the Australian Technical Advisory Group on Immunisation (ATAGI) also references a study reporting that COVID-19 vaccines may be associated with a small and temporary change in menstrual cycle length. Other regulators including the MHRA (UK) and Medsafe (New Zealand) have statements regarding

	menstrual irregularities and COVID-19 vaccinations expressing that the issue has been reviewed and there is currently insufficient evidence of an association, but it will continue to be monitored.
Quality of cases reported to the TGA	Due to the high number of reports of menstrual irregularities associated with COVID-19 vaccines in AEMS, a review of each individual report could not be undertaken. A targeted review of 27 reports coded as serious, life threatening, were reviewed. The overall minimal level of detail and low quality of reports provides limited support of an association. Time to onset information was not available for 18 of the 27 reports reviewed in detail, and the amount of information provided in the case narratives was usually very limited, making most cases un-assessable in terms of causality assessment. Overall, the cases reported to the TGA were of poor quality. More than half the reports in AEMS were made by consumers (61.7%), with only a small proportion of reports made by health professionals (4.4%).
Characterisation of the risk / clustering of reports	As the focus of the TIP was menstrual irregularities in women of reproductive age, females aged ≥60 years or <8 years of age were excluded from analysis of AEMS data. The median age of reports was 36 years (range 8-59* years), noting that 262 reports did not have an age provided. The majority of reports (79.3%) were related to Comirnaty. Over a third of reports (n=1011, 34.5%) co-reported HMB which has been included in the Australian PI for Spikevax and Comirnaty. Whilst not all reports could be reviewed, it is important to note that several reports did describe a recurrence of menstrual irregularities with subsequent doses of COVID-19 vaccine, providing evidence of positive rechallenge. Whilst this TIP focused on reproductive aged females, it was noted that there were several reports of post-menopausal bleeding and 1 report of vaginal haemorrhage in a 5-year-old. Consideration should be given to further investigating these reports in a separate TIP or mini-TIP.
Temporal relationship	Time to onset (TTO) information was **not** available for half of the reports (50.8%) in AEMS. A brief review of the TTO information for the 1,243 reports where TTO information was available, identified several issues with the information, notably that the onset of symptoms is the date recorded for the first symptom reported, which for multiple reports was for another reaction term (e.g. fever, headache) and in most cases did not relate to the onset of menstrual irregularities. Many of the reports referred to the following menstrual cycle being abnormal, with no direct mention of the time this was in days following vaccination. Given the significant limitations of the TTO data in relation to menstrual irregularities, an assessment of the TTO was not undertaken. It should be noted that where information about onset of symptoms was described, the changes in menstrual cycles were reported to occur after vaccination.
Specificity of the event	Abnormal uterine bleeding covers a wide range of changes to the menstrual cycle and has a large number of underlying causes. There are a number of potential confounders that may contribute to menstrual irregularities. Weight, stress and smoking are known factors to affect menstrual cycles and a large proportion of menstruating individuals experience changes in menstrual cycle at some point in

	their reproductive lifetime. Menstrual irregularities have also been associated with infection with SARS-CoV-2.
Biological plausibility	Several menstrual disorders are related to disturbances in the hypothalamic-pituitary-ovarian axis (HPO axis) which can be caused by multiple different factors including stress, viral infections, and immunological influences. It has been theorized that vaccination could trigger immunological responses that affect the HPO axis and hormones regulating the menstrual cycle or that immune mediated effects following vaccination could have effects on cells lining the uterus.
Health consequences	Only a small proportion of reports of abnormal uterine bleeding/menstrual irregularities in AEMS (12.7%) were reported as being serious with no reports describing a fatal outcome. It should be noted that for individual case reports coded as serious, the classification of serious could also be related to a co-reported reaction. The current evidence to date suggests that if there is an association between COVID-19 vaccines and menstrual irregularities the effect is small and temporary. Whilst the physical effects of menstrual disorders (excluding HMB) do not generally appear to be serious, abnormalities in menstrual cycles can cause phycological distress and discomfort and can be of particular concern for individuals planning pregnancy or dealing with fertility issues. These concerns may also contribute to vaccine hesitancy.
Impact on clinical practice	If valid, practitioners should be informed that menstrual irregularities may occur in menstruating individuals following vaccination. Awareness of a potential association would allow clinicians to counsel menstruating individuals about possible menstrual effects following vaccination and to seek further medical attention for ongoing issues or any red flag symptoms that may require further investigation. Reassurance that menstrual irregularities following vaccination do not affect fertility could increase public reassurance and acceptance of COVID-19 vaccines.
Concluding statement	The high volume of reports to pharmacovigilance databases and increasing number of studies in the published literature provide a growing evidence base for a possible association between menstrual disorders (excluding HMB) and COVID-19 vaccines, however the current evidence remains insufficient to strongly support a causal relationship. Establishing a causal relationship is challenging due to the wide number of conditions that are encapsulated by the terms abnormal uterine bleeding/menstrual irregularities and their various causes, the common incidence of menstrual cycle changes and the limitations of using adverse event reporting data that is subject to both under-reporting and stimulated reporting. The published literature on the association has mixed findings and significant limitations with the majority of studies to date being observational and subject to potential biases. Assessment of Australian specific data from AEMS is limited by the generally poor quality of reports, often with very limited information and no time to onset information. The diverse range of clinical entities that fall under the term abnormal uterine bleeding, and the large number of potential underlying causes makes determining a background incidence rate difficult and as such an observed versus expected analysis was not conducted and thus no comment on whether reports following vaccination are higher than expected in the background population can be made. The majority of reports of menstrual irregularities in AEMS are associated with Comirnaty. The majority of DPAR signals related to menstrual irregularities have

	also been related to Comirnaty, and s33 [redacted] Whilst there is insufficient evidence to request inclusion of menstrual irregularities in the product information document for Comirnaty at this stage, the sponsor should be requested to undertake a signal analysis for menstrual irregularities. Consideration should also be given to completing a TIP or mini-TIP on COVID-19 vaccines and abnormal uterine bleeding outside the reproductive age group.

Priority

Medium

Internal MO5/Stream Lead/MaVIS Issues Meeting Advice *(not for external release at this time)*

1:52pm, 24/07/23: The Director of Vaccine STRS endorses the recommendations outlined above (unchanged).

Additional factors to be considered	
Media/minister/consumer enquiries	
Political/internal organisational/whole of government considerations	

Internal Recommendation *(not for external release at this time)*

It is recommended that this signal be referred to Regulatory Outcomes Stream (ROS) to request sponsor of Comirnaty (Pfizer) to undertake signal assessment.

It is recommended that a mini-TIP be undertaken on COVID-19 vaccines and abnormal uterine bleeding outside the reproductive age group.

DISCLAIMER:

- **The purpose of this review process is to provide a targeted assessment (at a point in time) of the described vaccine-event pair to assist with triage of workflow. It does not constitute a full evaluation nor a regulatory decision.**

- **There are limitations of th79e data, methodology and pandemic-related factors which should be considered when interpreting this analysis and referencing the recommendations. In summary, passive or spontaneous reporting systems (SRS) have limitations including potential under-reporting of cases and poor data quality (such as missing information about the time period between vaccination and onset of symptoms and lack of medical verification in some reports). Therefore, SRS are appropriate for use in signal detection rather than formal hypothesis testing. Observed versus expected (OvE) and reporting rate analyses using data from SRS are also therefore limited in the same way. Furthermore, determining the appropriate background rate to use in OvE analyses is difficult, and there are inherent problems in applying historical background rates to determine expected cases for comparison with more recent observed cases, which may be exacerbated by pandemic related factors. Case definition criteria, such as the Brighton collaboration Case definitions, are used to increase the diagnostic certainty of reports, but their application to data from SRS is limited when insufficient information is provided, and they may not capture all variants of a disease/clinical entity.**

- **It should also be noted, that as the pandemic and the vaccine uptake evolves, large population-based observational studies from healthcare networks that can combine information from vaccination**

records and healthcare system diagnoses may provide a more accurate picture of real-world events than SRS and may eventually provide more useful information than spontaneously reported data about the incidence of the AE in unvaccinated populations compared to those vaccinated with this vaccine.

1. List of abbreviations

Abbreviation	Meaning
ACCESS	Australia-Canada-Singapore-Switzerland-United Kingdom (consortium)
ADR/AE	Adverse Drug Reaction / Adverse Event
AEFI	Adverse Event Following Immunisation
AEMS	Adverse Event Management System
AESI	Adverse Event of Special Interest
AIR	Australian Immunisation Register
ARTG	Australian Register of Therapeutic Goods
ATAGI	Australian Technical Advisory Group on Immunisation
ATC	Anatomical Therapeutic Chemical (classification system)
AUB	Abnormal Uterine Bleeding
CMI	Consumer Medicine Information
COVID-19	Coronavirus disease 2019
DHCPL	Dear Healthcare Professional Letter
EMA	European Medicines Agency (European Union)
FDA	Food and Drug Administration (United States)
GACVS	Global Advisory Committee on Vaccine Safety
HMB	Heavy Menstrual Bleeding
IC	Information Component
ICMRA	International Coalition of Medicines Regulatory Authorities
IPMST	International Post Market Surveillance Teleconference
MaVIS	Medicines and Vaccines Investigation and Surveillance
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency (United Kingdom)
MSSR	Monthly Safety Summary Report
MSU	Medicines Safety Update

NCIRS	National Centre for Immunisation Research and Surveillance
O/E	Observed vs. Expected (analysis)
PCD	Public Case Details
PI	Product Information
PRAC	Pharmacovigilance Risk Assessment Committee
PRR	Proportional Reporting Ratio
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
RMP	Risk Management Plan
ROS	Regulatory Outcomes Stream
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SPC/SmPC	Summary of Product Characteristics
SSR	Safety Summary Report
STRS	Surveillance and Targeted Review Stream
TIP	Targeted Investigation Process
VERA	Vaccine Epidemiology and Rapid Assessment
VSIG	Vaccine Safety Investigation Group
WHO-UMC	World Health Organisation – Uppsala Monitoring Centre

2. Vaccine information

Indication(s)	COVID-19 Vaccines VAXZEVRIA ChAdOx 1-S: Provisional approval for active immunisation of individual ≥ 18 years old for the prevention of COVID-19 caused by SARS-CoV-2. The TGA provisionally approved it for use in Australia on 15 February 2021 (primary vaccination course), and 8 February 2022 (booster dose for 18 years and over). COMIRNATY (BNT162b2 [mRNA]) COVID-19 Vaccine Pfizer: Provisional approval for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months of age and older. The TGA provisionally approved it for use in Australia on 25 January 2021 (for 16 years and over), 22 July 2021 (for 12 years and over), 26 October 2021 (booster dose for 18 years and over), 3 December 2021 (for 5 years and over), 27 January 2022 (booster dose for 16 to 17 years), 7 April 2022 (booster dose for 12 to 15 yeas), 20 September 2022 (booster dose for 5 to 11 years) and 29 September 2022 (for 6 months and over). SPIKEVAX (elasomeran) COVID-19 VACCINE: Provisional approval for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months of age and older. The TGA provisionally approved it for use in Australia on

	9 August 2021 (for 18 years and over), 3 September 2021 (for 12 years and over), 7 December 2021 (booster dose for 18 years and over), 17 February 2022 (for 6 years and over), 19 July 2022 (for 6 months and over) and 19 October 2022 (booster dose for 12 years and over). NUVAXOVID (SARS-COV-2 RS [NVX-COV2373]): Provisional approval for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in individuals 12 years of age and older. The TGA provisionally approved it for use in Australia on 19 January 2022 (for 18 years and over), 9 June 2022 (booster dose for 18 years and over), and 22 July 2022 (for 12 years and over). SPIKEVAX Bivalent Original/Omicron (elasomeran/imelasomeran) COVID-19 vaccine: Provisional approval as a booster dose for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in individuals 18 years of age and older. The TGA provisionally approved it for use in Australia on 29 August 2022 (booster dose for 18 years and over).
Vaccine roll-out status	The Australian Technical Advisory Group on Immunisation (ATAGI) has made recommendations on the use of COVID-19 vaccines in Australia. These were last updated 21 March 2023 (TRIM D23-5332717). **Primary vaccination course recommendations** COVID-19 vaccination is recommended for all people aged 5 years or older to protect against COVID-19. COVID-19 vaccination is recommended for children aged 6 months to under 5 years with severe immunocompromise, disability, and those who have complex and/or multiple health conditions that increase the risk of severe COVID-19. For most people, a primary vaccination course consists of 2 doses. A third primary dose is recommended for people aged 6 months or older with severe immunocompromise. As of March 2023, Moderna ≥6 years formulation (red cap) and AstraZeneca COVID-19 vaccines are no longer available in Australia. **Pregnant women** Pfizer original ≥12 years formulation (purple cap) is the recommended vaccines for primary course vaccination in pregnancy. There are substantial data on its safe use in pregnancy. Novavax can also be used for a primary course in pregnancy. There are no immunogenicity or safety data for this vaccine in pregnancy but there are no theoretical safety concerns. **Booster dose recommendations** A booster is recommended for: - All adults aged 65 years and over - Adults aged 18-64 years who have medical comorbidities that increase their risk of severe COVID-19, or disability with significant or complex health needs. ATAGI advises that a booster dose is not recommended at this time for children and adolescents aged under the age of 18 who do not have any risk factors for severe COVID-19. **Booster dose: vaccine preference recommendations** ATAGI expects that all currently available COVID-19 vaccines will provide a benefit however bivalent mRNA booster vaccines are preferred.
Mechanism of action	VAXZEVRIA ChAdOx 1-S is a recombinant replication-defective chimpanzee adenovirus ChAdOx1, carrying a gene encoding the SARS-CoV-2 spike (S) surface

	glycoprotein. Following administration, the S glycoprotein is expressed locally, stimulating neutralising antibody and cellular immune responses. COMIRNATY (BNT162b2 [mRNA]) COVID-19 Vaccine Pfizer comprises a nucleoside-modified messenger RNA (modRNA) encoding the viral spike glycoprotein (S) of SARS-CoV-2. The RNA is encapsulated in lipid nanoparticles (LNPs), which enables entry into host cells, expression of the S protein, and elicitation of both antibody and cellular immune responses. SPIKEVAX (elasomeran) COVID-19 VACCINE contains messenger ribonucleic acid (mRNA) encapsulated in lipid nanoparticles. The mRNA encodes for the full-length SARS-CoV-2 spike protein modified with 2 proline substitutions within the heptad repeat 1 domain (S-2P) to stabilise the spike protein into a prefusion conformation. Following administration, the lipid nanoparticle deliver the mRNA sequence into cells for translation, expression of the viral spike protein, and elicitation of both antibody and cellular immune responses. SPIKEVAX (Elasomeran and imelasomeran) COVID-19 vaccine contains mRNA encapsulated in lipid nanoparticles. The mRNA encodes for the full-length SARS-CoV-2 spike protein modified with 2 proline substitutions within the heptad repeat 1 domain (S-2P) to stabilise the spike protein into a prefusion conformation. After intramuscular injection, cells at the injection site and the draining lymph nodes take up the lipid nanoparticle, effectively delivering the mRNA sequence into cells for translation into viral spike protein. The expressed, membrane-bound spike protein of SARS-CoV-2 is then recognised by immune cells as a foreign antigen. This elicits both T-cell and B-cell responses to generate neutralising antibodies, which may contribute to protection against COVID-19. NUVAXOVID (SARS-COV-2 RS [NVX-COV2373]) contains the SARS-CoV-2 spike protein (produced by recombinant DNA technology using a baculovirus expressions system in an insect line that is derived from Sf9 cells of the Spodoptera frugiperda species) and is adjuvanted with Matrix-M (which contain Quillaja Saponaria saponins fraction A and fraction C).

3. Adverse event information

Signal Source	Several signals related to menstrual irregularities and abnormal menstruation first flagged on the May-June 2022 DPAR (TRIM D22-5830538) with the PRR for relevant signal pairs summarised in table 1 below. Most of these pairs are related to Comirnaty, with variations of these signal pairs continuing to flag on all subsequent DPARs (see tables 2-4). The signals were discussed again at a vaccine STRS team meeting following review of the November-December 2022 DPAR, and in light of update literature on the topic and the inclusion of heavy menstrual bleeding (HMB) to the EMA summary of product characteristics and MHRA summary of product characteristics, it was decided that a high priority TIP on menstrual irregularities be undertaken with a view to potentially include menstrual irregularity in the PI for relevant COVID-19 vaccines (TRIM D23-5083438). In addition to this at the Jurisdictional Immunisation Coordinators (JIC) Teleconference s22 [redacted] Cases of breakthrough bleeding in post-menopausal women which had worried one of the gynaecologists SAEFVIC was working with was also discussed (TRIM D23-5265922). However, this was discussed at a vaccine signal and targeted review stream team meeting and determined to be beyond the scope of this TIP.

Table 1: Vaccine-AEFI pairs related to menstrual disorders that signalled on the May-June 2022 DPAR

Generic Name	Reaction	Cases (Total)	PRR
Elasomeran (mRNA)	Oligomenorrhoea	19	4.69
SARS-CoV-2 rS (NVX-CoV2373)	Amenorrhoea	4	6.96
tozinameran	Abnormal uterine bleeding	12	3.79
tozinameran	Amenorrhoea	112	4.65
tozinameran	Intermenstrual bleeding	283	5.80
tozinameran	Menstrual disorder	2084	6.11
tozinameran	Menstruation delayed	166	7.70
tozinameran	Menstruation irregular	647	6.08
tozinameran	Oligomenorrhoea	96	3.79
tozinameran	Polymenorrhoea	158	8.90

Table 2: Vaccine-AEFI pairs related to menstrual disorders that signalled on the July-August 2022 DPAR

Generic Name	Reaction	Cases (Total)	PRR
SARS-CoV-2 rS (NVX-CoV2373)	Amenorrhoea	5	7.62
SARS-CoV-2 rS (NVX-CoV2373)	Menstruation irregular	11	3.11
tozinameran	Amenorrhoea	116	4.52
tozinameran	Intermenstrual bleeding	285	5.63
tozinameran	Menstrual disorder	2127	6.04
tozinameran	Menstruation delayed	170	7.57
tozinameran	Menstruation irregular	656	6.02
tozinameran	Oligomenorrhoea	100	3.90
tozinameran	Polymenorrhoea	166	9.25

Table 3: Vaccine-AEFI pairs related to menstrual disorders that signalled on the September-October 2022 DPAR

Generic Name	Reaction	Cases (Total)	PRR
tozinameran	Amenorrhoea	118	4.49
tozinameran	Menstrual disorder	2140	6.06
tozinameran	Menstruation delayed	176	7.85
tozinameran	Menstruation irregular	660	6.06
tozinameran	Oligomenorrhoea	101	3.94
tozinameran	Polymenorrhoea	170	9.48

Table 4: Vaccine-AEFI pairs related to menstrual disorders that signalled on the November-December 2022 DPAR (TRIM D23-5037468)

Generic Name	Reaction	Cases (Total)	PRR

tozinameran	Menstrual disorder	2153	6.0
tozinameran	Menstruation delayed	179	8.0
tozinameran	Oligomenorrhoea	102	3.8
tozinameran	Polymenorrhoea	171	8.9

Previous TIPs related to menstrual disorders are summarised in table 5 below.

Table 5: Pervious TIPs related to COVID-19 vaccines and menstrual disorders

Signal	TRIM link	Month/Year of evaluation	Outcome
Comirnaty & Vaxzevria and menstrual bleeding disorder	D21-2947788	August 2021	Monitor
COVID-19 vaccines and menstrual disorder	D22-5024968	January 2022	Monitor
Comirnaty & Spikevax and heavy menstrual bleeding	D22-6166179	December 2022	Regulatory action – PI update request underway

AESI status

Menstrual irregularities or disorders and related terms are not AESI.

AEFI

Menstrual irregularities or menstrual disorders cover a wide range of conditions, that are more appropriately covered under the term abnormal uterine bleeding (AUB), which has a clear medical definition, although the terms are often used interchangeably, including in this document. The term abnormal uterine bleeding (AUB) covers a broad range of terms related to irregularities in menstrual cycles and refers to bleeding from the uterus that is abnormal in regularity, frequency, duration and/or quantity.[1] Some known factors that can cause menstrual cycle irregularity include obesity, smoking and stress. [2]

It is estimated between 3% to 30% of reproductive aged women will experience AUB, with irregularities most commonly occurring at menarche and around perimenopause.[1] The true prevalence of AUB may actually be higher than estimated, as many studies on the prevalence of AUB only include heavy menstrual bleeding (HMB). [1]

The causes of AUB are usually divided into structural causes (e.g. polyps, leiomyomas and malignancies) and non-structural causes (e.g. disorders affect the hypothalamic-pituitary-ovarian (HPO) axis, ovulatory dysfunction, endometrial disorders and not otherwise classified diseases such as pelvic inflammatory disease). [1] Treatment and resolution of AUB will vary depending on the underlying cause. [1]

Public concerns over menstrual irregularities and potential effects on fertility were highlighted following the implementation of COVID-19 vaccination programs around the world. Katz et al. reported a surge in Google searches related to 'menstrual irregularities and COVID vaccine' following the introduction of COVID-19 vaccination programs in English speaking countries. [3] Vaccine safety concerns about

	effects on reproduction and fertility can contribute to public mistrust and vaccine hesitancy.
No. of AEFI reports	As per the discussion at the Vaccine Surveillance and Targeted Review (vSTRS) team meeting, the High Level Group Terms (HLGT) 'menstrual cycle and uterine bleeding disorders NEC',Concerns over 'menstruation with decreased bleeding' and 'menstruation with increased bleeding' were used to generate a list of preferred terms (PTs), with specific PTs related to abnormal menstrual cycle and abnormal bleeding selected, excluding PTs related to heavy menstrual bleeding (HMB) or pain. The following list was generated, with bolded terms used in the subsequent Adverse Events Management System (AEMS) database search. - Abnormal menstrual clots - **Abnormal uterine bleeding** - **Abnormal withdrawal bleeding** - **Anovulatory cycle** - **Bleeding anovulatory** - Delayed menarche - Dysmenorrhoea - **Intermenstrual bleeding** - Menstrual discomfort - **Menstrual disorder** - Menstrual headache - **Menstruation irregular** - Premature menarche - Premenstrual dysphoric disorder - Premenstrual pain - Premenstrual syndrome - **Retrograde menstruation** - **Withdrawal bleed** - **Amenorrhoea** - **Hypomenorrhea** - **Menstruation delayed** - **Oligomenorrhoea** - **Pituitary amenorrhoea** - Heavy menstrual bleeding - **Menometrorrhagia** - **Polymenorrhagia** - **Polymenorrhoea** On 22nd May 2023, a search of the AEMS database was conducted using the COVID-19 vaccine safety app in Qlik with default bookmark and the PTs highlighted above. This search identified 2, 934 case reports. Of these reports: - 2707 reports of menstrual disorder - 830 reports of menstruation irregular - 359 reports of intermenstrual bleeding - 215 reports of menstruation delayed - 203 reports of polymenorrhoea - 155 reports of amenorrhoea - 141 reports oligomenorrhoea - 16 reports of abnormal uterine bleeding - 14 reports of hypomenorrhoea - 13 reports of mentometrorrhagia - 4 reports of polymenorrhagia

	- 3 reports of anovulatory cycle Of note, over a third of reports (n=1011, 34.5%) co-reported HMB. Most reports were related to Comirnaty (n =2329, 79.3%). Of the remaining reports, 342 were related to Vaxzevria, 230 to Spikevax, 29 to Nuvaxovid, 14 to COVID-19 vaccine trade name not specified, one to Spikevax bivalent vaccine (TNS) and one to Spikevax bivalent vaccine (elasomeran/imelasomeran). Note, when breaking the number of reports down by vaccine type the total number is 2,946 as some vaccines given in a dose series have been coded as concomitant and will both be coded for and associated with the same AEFI report. By the end of May 2023, there was a total of 53,510 AEFI reports related to Comirnaty in females. Of these AEFI reports, 2127 (4%) were for menstrual disorder, making menstrual disorder the 22nd most commonly reported AEFI for Comirnaty in females.
Characterisation of the risk/ clustering of reports	Of the 2,934 reports, 374 (12.7%) were reported as being serious. Of these, 101 were considered serious because of prolonged hospitalisation, 64 as 'other' serious condition, 45 as disabling or incapacitating and 27 were reported as life-threatening. No reports described a fatal outcome. Of the total number of AEFI reports for PTs related to menstrual irregularities, 208 reported management of the event by emergency department (ED) visit or hospital admission, with 417 reporting seeking GP assessment. It is important to note however, that management of event options are not mutually exclusive, and some individuals may have sought GP assessment and presented to ED/admitted hospital. Furthermore, management of event may be related to another AEFI reaction that was co-reported with the PTs selected in this search rather than to the specific menstrual irregularity related PT from this search. 56 reports were from individuals who identified as being Aboriginal and/or Torres Strait Islander. The median age of reports was 36 years (range 8-59* years), noting that 262 reports did not have an age provided. * As the focus of the TIP was menstrual irregularities in women of reproductive age, so given that average age of menopause in Australia is 51, with most women experiencing menopause between 45 and 60 years of age, [3] thirty-five reports in females aged ≥60 years of age were excluded from analysis as it was assumed they were likely to be post-menopausal. A further 75 reports were excluded as they co-reported the reaction term 'post-menopausal haemorrhage'. Of the 2,813 reports following exclusion of post-menopausal reports, 61.7% (n=1737) were reports made by patients/consumers. Only a small proportion (4.4%, n = 124) were reported by health care professionals. <u>Time to onset</u> Of the 2,813 reports following exclusion of post-menopausal reports, time to onset (TTO) information was **not** available for half of the reports (n =1430, 50.8%). A further 137 reports had a negative time to onset (likely as result of the method used to remove dose duplicates from the data) and were not included in calculation of the average TTO. A brief review of the TTO information for the 1,243 reports where TTO information was available identified several issues with the information, notably that the onset of symptoms is the date recorded for the first symptom reported, which for multiple

reports was for another reaction term (e.g. fever, headache) and in most cases did not relate to the onset of menstrual irregularities. Many of the reports referred to the following menstrual cycle being abnormal, with no direct mention of the time this was in days following vaccination. Given the significant limitations of the TTO data in relation to menstrual irregularities, an assessment of the TTO was not undertaken.

Vaccine dose relationship

It should be noted that dose data is limited by the way it was initially recorded for COVID-19 vaccines in CRM, whereby reports describing multiple doses of COVID-19 vaccines had each vaccine dose reported recorded as suspect. This led to multiple vaccine doses being list for the same PTs in CRM and Qlik. When analysing the data in AEMS, duplicate records for the same AEFI report relating to the multiple doses in series have to be removed (noting they still relate to only one ICSR). Given the large volume of reports, for this analysis duplicate reports were removed en masse and not through individual assessment of each report to determine which dose in series the AEFI report related to. This was done by assuming the report was related to highest dose number (most recent) COVID-19 vaccine in series and previous doses were removed. In view of this, information on dose association should be interpreted with caution.

Dose information was available for 1,761 reports, menstrual irregularities were most commonly reported in association with the second dose of a COVID-19 vaccine containing vaccine (n = 825, 46.8%).

Whilst a review of every case narrative was not possible due to the high number of reports, a brief review of reports noted that multiple case narratives described menstrual irregularities following the first dose of COVID-19 vaccine and again following the second dose of COVID-19 vaccine showing evidence of **positive rechallenge**.

Summary/ assessment of AEFI reports

Summary of overall findings of the brief causality assessments

Due to the high number of reports, each report could not be assessed individually, so a subset of 27 reports that were reported as serious based on serious criteria 'life-threatening' were reviewed and are summarised in the table below. It is important to note that the assignment of 'serious' to the case report for most of these cases either related to another AEFI that was co-reported, or was selected by the reporter (primarily consumers) without clear information in the case narrative to explain how the condition was life-threatening.

The overall low quality of reports in AEMS and limited detail provided limited support for an association. TTO information was not available for 18 of the 27 reports reviewed in detail, and the amount of information provided in the case narratives was usually very limited, making most cases un-assessable in terms of causality assessment. Most of the reports (n=24) were from consumers, with only three reports from health professionals.

ADR Case	Age S/T	TTO/Dose/ Outcome	Clinical details	Causality assessment*
AU-TGA-633690	17	Comirnaty	s22	Un-assessable

			Dose s22 TTO s22	s22	
	AU-TGA-684440	21	Spikevax Dose s22 TTO s22		Un-assessable
	AU-TGA-721269	27	Comirnaty Dose s22 TTO s22		Un-assessable
	AU-TGA-639202	28	Comirnaty s22 TTO s22		Possible
	AU-TGA-692191	30	Comirnaty Dose s22 TTO s22		Possible
	AU-TGA-0000704376 - 20221109224111	30	Comirnaty Dose s22 TTO s22		Possible
	AU-TGA-704068	30	Comirnaty		Un-assessable

			Dose s22 TTO s22	s22	
	AU-TGA-660424	32	Comirnaty Dose s22 TTO s22		Possible
	AU-TGA-664009	34	Comirnaty Dose s22 TTO s22		Un-assessable
	AU-TGA-646709	35	Comirnaty Dose s22 TTO s22		Un-assessable
	AU-TGA-757186	35	Comirnaty Dose s22 TTO s22		Un-assessable
	AU-TGA-702603	35	Comirnaty Dose s22 TTO s22		Un-assessable
	AU-TGA-627418	35	Comirnaty Dose s22		Un-assessable

			TTO s22	s22	
	AU-TGA-669964	37	Comirnaty Dose s22 TTO s22 s22		Possible
	AU-TGA-641659	37	Comirnaty Dose s22 TTO s22 s22		Un-assessable
	AU-TGA-709634	37	Comirnaty Dose s2 s22 TTO s22		Un-assessable
	AU-TGA-740168	38	Comirnaty Dose s22 TTO s22		Possible

			s22	
AU-TGA-736954	38	Comirnaty Dose s22 TTO s22 s22		Un-assessable
AU-TGA-717602	38	Comirnaty Dose s22 TTO s22		Un-assessable
AU-TGA-726809	39	Comirnaty Dose s22 TTO s22 s22		Un-assessable
AU-TGA-681049	39	Comirnaty Dose s22 TTO s22		Un-assessable
AU-TGA-729724	40	Comirnaty Dose s22 TTO s22		Un-assessable

				s22	
	AU-TGA-696652	41	Comirnaty Dose s22 TTO s22		Un-assessable
	AU-TGA-753117	46	Comirnaty Dose s22 TTO s22		Possible
	AU-TGA-721710	47	Comirnaty Dose s22 TTO s22		Un-assessable
	AU-TGA-699013	47	Comirnaty Dose s22 TTO s22		Unlikely
	AU-TGA-702965	56	Comirnaty Dose s22		Un-assessable

			TTO s22	s22 [redacted]	

*Based on causality assessment criteria at TRIM D23-5372930

Magnitude of signal

DPAR

The following terms related to menstrual irregularities and AUB signalled as disproportionate in the March-April 2023 DPAR (TRIM D23-5343414).

Reaction (PT)	Reaction term	PRR	PRR LCI	IC_{025}
Nuvaxovid	Menstruation irregular	**3.31**	1.92	0.66
Comirnaty	Menstrual disorder	**6.06**	5.53	0.96
Comirnaty	Menstruation irregular	**6.03**	5.10	0.90
Comirnaty	Oligomenorrhoea	**3.88**	2.71	0.54

Reporting Rate

A reporting rate for menstrual irregularities was calculated for each COVID-19 vaccines using AEMS data (with post-menopausal cases excluded) and AIR dose data for females aged 8 to 59 years (data extract from 16 May 2023 TRIM D23-5388915).

Signal/AESI	Vaccine name	Observed cases*	Reporting rate per 100,000 doses
Menstrual irregularities (combined PTs: Abnormal uterine bleeding, Abnormal withdrawal bleeding,	Comirnaty	2258	12.6
	Vaxzevria	304	14.1
	Spikevax	228	12.5
	Nuvaxovid	28	28.5

	Anovulatory cycle, Bleeding anovulatory, Intermenstrual bleeding, Menstrual disorder, Menstruation irregular, Retrograde menstruation, Withdrawal bleed, Amenorrhoea, Hypomenorrhea, Menstruation delayed, Oligomenorrhoea, Pituitary amenorrhoea, Menometrorrhagia, Polymenorrhagia, Polymenorrhoea)	Spikevax bivlanet (Elasomeran/imelasomeran)	1	2.3

*Observed cases after exclusion of post-menopausal reports, n = 2813, however total for all vaccines in this table = 2819 as some AEFI reports have two or more COVID-19 vaccines reported as suspect, due to previous AEMDS coding convention whereby multiple COVID-19 vaccines doses in series mentioned in a case report were coded as susect. This may lead to a slight overestimation of vaccine doses for some vaccines. A further 11 reports were for COVID-19 vaccine trade name not specified so no reporting rate was calculated for these.

The reporting rate of menstrual irregularities for the COVID-19 vaccines was rare (≥ 1/10,000 to < 1/1,000). The reporting rates for Comirnaty, Vaxzevria and Spikevax were similar, with the reporting rate for Nuvaxovid being relatively higher, noting the overall number of reports associated with Nuvaxovid was low (n = 28).

O/E Analysis

Due to heterogeneity of conditions that fall under the category of AUB a background incidence rate for AUB as a broader term was not identified and so an observed versus expected analysis was not conducted.

4. Regulatory surveillance

Local, including:	**Product Information (PI)**
PI, Sponsor's PSUR/MSSR, and applicable clinical guidance	Under section 4.8, Adverse events, the **Comirnaty PI** (Version: pfpcobii20223, last updated 27/2/23, TRIM D23-5448382), **Spikevax PI** (SPIKEVAX_PI_v16.0_24 Apr23, last updated 24/4/23, TRIM D23-5448802), **Spikevax Bivalent** (elasomeran/imelasomeran) (SPIKEVAX BIVALENT ORIGINAL/OMICRON_PI_v4.1_21Feb23, last updated 21/2/23, TRIM D23-5448971) and **Spikevax Bivalent** (elasomeran/davesomeran) (SPIKEVAX BIVALENT ORIGINAL/OMICRON BA.4-5_PI_v2.0_20Feb23, last updated 20/2/23, TRIM D23-5449020) include **Heavy Menstrual Bleeding** as an adverse event reported from post marketing experience, noting most cases appear to be non-serious and temporary in nature. There is no reference to other menstrual irregularities or disorders.

The Nuvaxovid PI (version 7, last updated 25/1/23, TRIM D23-5448650) and Vaxzevria PI (Doc ID-004490138 v22, last updated 17/4/23, TRIM D23-5448710) do not include HMB or reference to any other menstrual disorders.

Applicable clinical guidance

The Department of Health has an information sheet on COVID-19 vaccines and menstruation (last updated 3 November 2022, TRIM D23-5452702) that references the study by Edelman *et al.* and states that "*There is evidence of a very small change to menstrual cycles in the month of vaccination*".

Sponsor's PSUR/MSSR/SSR

Comirnaty

The Periodic Safety Update Report (PSUR) for Comirnaty covering the period 16 January to 15 February 2023 (TRIM D23-5202162) states the following in relation to menstrual irregularities:

Signal	Source	Data	Action
Menstrual irregularities	Spontaneous Data: Non statistical Reports; Other (SRL review in response to PRAC signal with Amenorrhea and Heavy Menstrual Bleeding)	Post-authorization safety data, clinical study safety data, Literature review	Under Evaluation. Following review of HMB and Amenorrhea (EMA PRAC signals), the MAH determined that the broader concept of menstrual irregularities (not limited to HMB and Amenorrhea) will be evaluated.

Vaxzevria

In the Vaxzevria PSUR covering the period 29 June 2022 to 28 December 2022, menstrual disorders are discussed undersection 15.2.2 of the document (TRIM D23-5191326).

In the assessment report received from the PRAC EMA (PRAC PAR (EMEA/H/C/PSUSA/00010912/202206) for the VAXZEVRIA PBRER (review period: 29 December 2021 to 28 June 2022), further information on the topic of Menstrual disorders has been requested as follows:

The MAH is requested to provide and discuss an updated literature review of Menstrual disorders. Besides, the MAH is requested to further discuss the serious cases requiring hospitalization and the cases resulting in death.

A cumulative search till 28 December 2022 of the AstraZeneca Global Safety Database for Menstrual disorders with VAXZEVRIA and retrieved a total of 21651 case reports with 28063 events of Menstrual disorders.

Out of 21651 cases, 423 cases with 520 events of Menstrual disorders were reported with the seriousness criteria of hospitalisation and 2 further cases with 2 events resulted in death.

The MAH summary and conclusion from the review of cases and literature review was:

Upon further review of the serious cases requiring hospitalization and the cases resulting in death, there was insufficient information on menstrual history, investigations performed, and treatment details available in these reports. These findings do not provide more insight on the possible relationship between VAXZEVRIA and menstrual disorders.

From the review of the literature, many of the literature available recommended future work to examine the hypothesized biological mechanisms that may explain an association between COVID-19 vaccination and menstrual disorders.

In summary, the review of available data from spontaneous reports and literature did not identify an index case or other evidence of a new or emerging signal.

Conclusion

The information from this updated cumulative review found insufficient evidence for a new or emerging signal regarding Menstrual disorders and VAXZEVRIA. No changes to the CDS or RMP are recommended, and Menstrual disorders will continue to be monitored as part of AstraZeneca's ongoing surveillance activities.

Spikevax

The Spikevax PSUR covering the period 19 June 2022 to 17 December 2022 (TRIM D23-5158315) states that during the reporting period, Health Authorities (HAs) requested evaluation of a signal for Amenorrhea (re-evaluated) which was ongoing at the DLP of the reporting period.

Signal term	Date detected	Status	Source	Reason for evaluation and summary of key data	Action(s)
Amenorrhoea (re-evaluation)	13 Jun 2022	Ongoing	Health Authority Request	A signal of amenorrhea was evaluated as a refuted signal in Mar 2022 (EPITT No 19781). A new signal for amenorrhea was opened based on PRAC Signal AR (dated 13 Jun 2022) where PRAC concluded that the current evidence is insufficient to warrant an update to the product information at present and agreed that the MAH of COVD-19 mRNA vaccine (nucleoside modified) elasomeran, should provide an updated cumulative review of amenorrhea events postvaccination in the PSUR with the DLP of 17 Dec 2022.	Evaluation ongoing

	Nuvaxovid The Nuvaxovid MSSR covering the period 20 December 2022 to 28 February 2023 (TRIM D22-5271483) reported that menstrual disorders include in a list of safety topics where cumulative cases in the global safety database were reviewed and ***no safety observation was identified.***
US FDA	**Label** None of the FDA labels for Comirnaty, Spikevax or Nuvaxovid, include any reference to menstrual disorders. **Pfizer BioNtech** label Document Id: 94f5323b-03fb-4062-825b-0240121f7958, last updated 5/2023, TRIM D23-5454591 **Pfizer bivalent,** document Id: 27fa1e44-d94a-40ad-a397-860174959b97, last updated 28 April 2023, TRIM D23-5455824 **Moderna original** label, last updated May 2023, TRIM D23-5454724 **Moderna bivalent** (Omicron BA.4/BA.5) label, last updated 8/12/2022 TRIM D23-5454682 **Novovax** label, last updated 28/3/2023 TRIM D23-5454721 **Relevant regulatory action** The CDC provides the following information regarding COVID-19 vaccines and menstrual disorders in their section frequently asked questions (TRIM D23-5452750) *Do COVID-19 vaccines affect your menstrual cycle (period)?* *Results from recent research studies show that people who menstruate may observe small, temporary changes in menstruation after COVID-19 vaccination, including:* - ***Longer duration of menstrual periods*** - ***Shorter intervals between periods*** - ***Heavier bleeding than usual*** *Despite these temporary changes in menstruation, there is no evidence that COVID-19 vaccines cause fertility problems.*
EU EMA	**Summary of Product Characteristics (SmPC)** The **tozinameran** SmPC (EMEA/H/C/005735 - II/0139, last updated 24/3/2023, TRIM D23-5495515) includes **HMB** under section 4.8 Post marketing experience, but **does not** include reference to any other menstrual disorders. The **Spikevax** SmPC (EMEA/H/C/005791 - II/0097/G, last updated 31/5/2023, TRIM D23-5495576) includes **HMB** under section 4.8 Post marketing experience, but **does not** include reference to any other menstrual disorders.

	The **Nuvaxovid** SmPC (Nuvaxovid - EMEA/H/C/005808 - II/0039/G, last updated 27/3/2023, TRIM D23-5495542) **does not** include any reference to any menstrual disorders. The **Vaxzevria** SmPC (EMEA/H/C/005675 - IA/0092/G, last updated 12/5/2023, TRIM D23-5495564) **does not** include any reference to any menstrual disorders. **Relevant regulatory action** At the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) meeting 24-27th October 2022, the EMA PRAC recommended that HMB should be added to the product information as a side effect of unknown frequency of the mRNA COVID-19 vaccines Comirnaty and Spikevax (TRIM D23-5455883). In December 2022, the TGA reviewed the EMA PRAC assessment of HMB (TRIM D22-6221680) and completed a summary of the signal assessment (TRIM D22-6227043). Following this, the TGA requested the sponsor to update the Australian product information documents for Comirnaty and Spikevax, which now both include HMB under section 4.8 The EMA PRAC assessment provided background information which included the previous assessment of the broader clinical issue of "menstrual disorders". The PRAC noted that "*the issue of menstrual disturbances is somewhat difficult to analyse, due to the range of clinical entities included, the difficulty in estimating their background incidences in relevant populations and the fact that reports are mainly from patients and lacking thorough clinical evaluation. Given the many different symptoms and reactions included in the topic "Menstrual disorders", the signalling MS NO finds it necessary to extract those reactions/patterns that we consider the most severe and evaluate these in separate signal procedures."* The EMA PRAC rappator for the signal assessment report in October 2022 estimated that based on their ICSRs menstrual disorders were by far the most commonly reported ADRs for women. They estimated through manual sampling and screening of incoming reports that since June 2021 when the signal was first raised, approximately 30% of reports submitted by women could be related to the issue of menstrual disturbances. A further important consideration noted when looking at menstrual irregularities was that "the absolute number of spontaneously reported cases is high, but this not unexpected taking into account the huge background incidence of menstrual disorders irrespective of COVID-19 vaccination, and the pandemic context with an unprecedented high number of administered doses of vaccines, and the large (social) media attention on this topic. Spontaneous reporting rates should be interpreted cautiously, as both underreporting and stimulated reporting [due to media attention] cannot be excluded. Confounding by (pre-)vaccination anxiety-/lockdown stress, undetected (corona)infections cannot be fully excluded at this moment. This led to the further evaluation of the more specific clinical entity of HMB which has since been added to the EMA PIs for Spikevax and Comirnaty. No further information about any potential further investigation by the EMA into other menstrual irregularities was identified at this point in time.
UK MHRA	**Summary of Product Characteristics (SPC)**

The **tozinameran** SPC (spc-doc_PLGB 53632-0006, last updated 22/5/2023, TRIM D23-5495872) includes **HMB** under section 4.8 Post authorisation experience, but **does not** include reference to any other menstrual disorders.

The **Spikevax** SPC (spc-doc_PLGB 53720-0002, last updated 2/5/2023, TRIM D23-5495939), Spikevax bivalent original/omicron BA.1 (spc-doc_PLGB 53720-0010, last updated 6/6/2023, TRIM D23-5495966) and Spikevax bivalent original.omicron BA.4-5 (spc-doc_PLGB 53720-0007, last updated 6/6/2023, TRIM D23-5495990) include **HMB** under section 4.8 Post marketing experience, but **does not** include reference to any other menstrual disorders.

The **Nuvaxovid** SPC (spc-doc_PLGB 54180-0002, last updated 6/6/2023, TRIM D23-5496001) **does not** include any reference to any menstrual disorders.

The **Vaxzevria** SPC (spc-doc_PLGB 17901-0355, last updated 12/5/2023, TRIM D23-5496054) **does not** include any reference to any menstrual disorders.

Relevant regulatory action

The last MHRA Coronavirus vaccine –summary of Yellow Card reporting updated on 8 March 2023 March 2023 (TRIM D23-5449134) commented on the specific safety topic of menstrual disorders and unexpected vaginal bleeding with the following:

Menstrual disorders (period problems) and unexpected vaginal bleeding

The MHRA has continued to review reports of suspected side effects of menstrual disorders (period problems) and unexpected vaginal bleeding following vaccination against COVID-19 in the UK. These reports are also being reviewed by the independent experts of the CHM's COVID-19 Vaccines Benefit Risk Expert Working Group and the Medicines for Women's Health Expert Advisory Group. Evidence from the most recent review suggested a possible association between the Pfizer and Moderna COVID-19 vaccines and heavy menstrual bleeding. The events were mostly non-serious and were temporary in nature. The product information for the Pfizer and Moderna COVID-19 vaccines has been updated to add heavy menstrual bleeding as a possible side effect. The rigorous evaluation completed to date does not support a link between COVID-19 vaccines and other changes to menstrual periods. There is no evidence to suggest that COVID-19 vaccines will affect fertility and your ability to have children.

Whilst uncomfortable or distressing, period problems are extremely common and stressful life events can disrupt menstrual periods. Changes to the menstrual cycle have also been reported following infection with COVID-19 and in people affected by long-COVID. General advice about period problems and/or unexpected vaginal bleeding is available from the NHS website. It is important that anyone experiencing changes to their periods that are unusual for them, persist over time, or has any new vaginal bleeding after the menopause, following COVID-19 vaccination, should contact their doctor. Anyone presenting with menstrual disorders and/or unexpected vaginal bleeding following COVID-19 vaccination should be treated according to clinical guidelines for these conditions, as usual.

From 1 September 2022 to 22 February 2023 a total of 182 suspected reactions relating to a variety of menstrual disorders have been reported after administration of the bivalent COVID-19 vaccines or COVID-19 vaccine Novavax including heavier than usual periods, delayed periods and unexpected vaginal bleeding. These

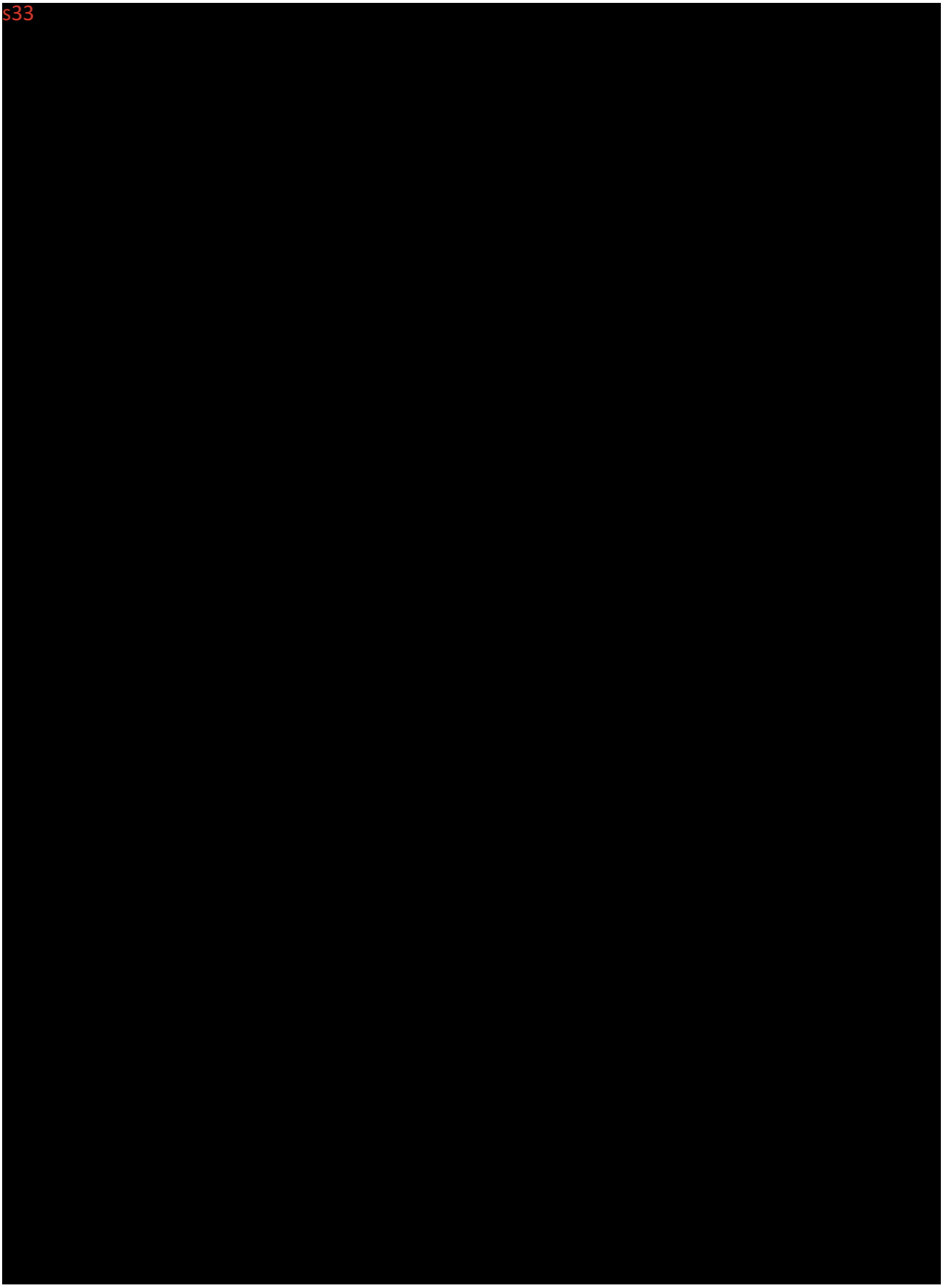
	suspected reactions have been reported in 167 individual Yellow Card reports (as each report may contain more than one suspected reaction). This is following approximately 1.7 million bivalent COVID-19 vaccine doses administered to women under 50 years of age up to 22 February 2023. The number of reports of menstrual disorders and vaginal bleeding is low in relation to both the number of people who have received COVID-19 vaccines to date and how common menstrual disorders are generally. *The MHRA will continue to closely review reports of suspected side effects of menstrual disorders and unexpected vaginal bleeding.*
Health Canada	**Product Monograph** None of the product monographs for Comirnaty, Vaxzevria, Spikevax or Nuvaxovid include reference to menstrual disorders. **Comirnaty** (02522454, last updated 31/3/2023, TRIM D23-5496224) **Spikevax** (02510014, last updated 12/01/2023, TRIM D23-5496321) **Spikevax bivalent** (elasomeran/imelasomeran) (02530252, last updated 23/2/2023, TRIM D23-5496336) **Spikevax bivalent** (elasomeran/davesomeran) (02532352, last updated 18/05/2023, TRIM D23-5496350) **Nuvaxovid** (02525364, last updated 31/3/2023, TRIM D23-5496304) **Vaxzevria** (02510847, last updated 14/12/2022, TRIM D23-5496282) **Relevant regulatory action** Health Canada's Reported side effects following COVID19 vaccines in Canada report (TRIM D23-5496389), last updated on June 9, 2023 with data up to and including May 26, 2023, did not include reference to menstrual irregularities.
NZ Medsafe	**Datasheet** None of the data sheets for Comirnaty, Vaxzevria, Spikevax or Nuvaxovid include reference to menstrual disorders. **Comirnaty** (Version: pfdcopii21222, last updated 7/12/2023, TRIM D23-5496572) Spikevax **Nuvaxovid** (Version 8, last updated 4/02/2022, TRIM D23-5496629) **Vaxzevria** (171122, last updated 17/11/2022, TRIM D23-5496659) **Relevant regulatory action** On 17 November 2021, Medsafe reported a monitoring communication 'Menstrual disorders and unexpected vaginal bleeding – Comirnaty (Pfizer COVID-19 vaccine)' The full communication is available at TRIM D23-5496687). *Summary*

	Medsafe has been investigating a potential link between vaccination with Comirnaty and menstrual disorders or unexpected vaginal bleeding. As a result of our review we can reassure healthcare professionals and members of the public that no link has been found with vaccination. *Regulator Action* *This issue was discussed with the COVID-19 Vaccine Independent Safety Monitoring Board (CV-ISMB) on 27 October 2021, who recommended Medsafe communicate their agreement with the conclusion that there is no evidence to support a link between menstrual disorders and Comirnaty administration.* *Medsafe will continue to monitor the rate and pattern of occurrence of this issue.*
Other international regulators (via ICMRA PV Network and ACCESS, WHO GACVS, IPMST)	The EMA discussed mRNA vaccines and HMB at the International Coalition of Medicines Regulatory Authorities (ICMRA) COVID-19 Vaccines Pharmacovigilance Network (VPN) Meeting #36 – 22 November 2022 (TRIM D23-5052531). *EMA provided VPN members an update on the recent recommendation from the Pharmacovigilance Risk Assessment Committee (PRAC) to add heavy menstrual bleeding to the product information as a side effect of unknown frequency for mRNA COVID-19 vaccines Comirnaty and Spikevax. Reported cases were found to be not serious and temporary in nature. A detailed assessment report on this will be published with the timeframe to be confirmed. The PRAC overview can be viewed at https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-24-27-october-2022* *A number of members have been following this issue closely and previous investigations had suggested that the rates were not higher than the background rate. TGA, s33 noted they were currently liaising with sponsors/applicants of mNRNA vaccines about this topic seeking their responses to the recommendation to consider if an update may be warranted.* The focus was again HMB rather than other menstrual disorders or irregularities and no meetings from 2023 to date appear to have discussed the issue of other menstrual disorders. There was no mention of menstrual irregularities in the most recently available committee report from the World Health Organisation Global Advisory Committee on Vaccine Safety (WHO GACVS) meeting, 14-16 December 2022 (TRIM D23-5495320).

5. Other information

s33 [redacted]

s33



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Literature	There have been several studies investigating the potential association between COVID-19 vaccines and menstrual irregularities, however, the available evidence to date is limited and conflicting. Whilst some studies have reported an increased incidence of menstrual irregularities following vaccination others have found no significant difference. Most of the studies are observational cross-sectional studies with many having possible biases in the study design, limiting the strength of evidence they provide. Those that did find an association general found a small increase in cycle length that appeared to be temporary and generally resolved by the following cycle. Further research is needed to determine whether there is a causal link between vaccination and menstrual cycle changes, particularly clinical trials for COVID-19 vaccines should include menstrual changes as an adverse event to monitor and report on. A literature search was conducted on 8/5/2023 using the PubMed database and search terms: ((((menstrual irregularities) OR (menstrual disturbances)) OR (menstrual cycle)) OR (menstrual disorder)) AND (COVID-19 vaccine). This search identified 74 journal articles (TRIM D23-5367442). Of these: - 31 were observational cross-sectional studies - 13 cohort studies (including one population level cohort study) - 12 not directly relevant - 6 reviews (1 systematic) - 5 letters to the editor/editorials/comments - 2 other (analysis of google searches and twitter/ analysis of VAERS AEFI data) - 1 case-control study - 1 self-controlled case series - 1 pre-test post-test quasi experiment evaluation - 1 meta-analysis - 1 duplicate report The majority of published papers identified in the literature search were observational cross-sectional studies, with most based on voluntary online surveys. These studies had several limitations including the potential for self-selection bias and recall bias, often small sample sizes and for many, very limited or absent details about participant recruitment. Several studies excluded menstruating individuals that had irregular menstrual cycles, which would exclude identifying an associations within this group which may already have predisposing factors for AUB.

Due to the large volume of published papers on the topic, not all papers could be reviewed, so the literature review focused on the systematic review, meta-analysis, population level cohort study and the quasi-experimental study and a selection of cohort studies.

Meta-analysis

A meta-analysis by Al Kadri *et al* (TRIM D23-5302283) including 16 epidemiologic studies found that following COVID-19 vaccination, the pooled prevalence of **menorrhagia** was **24.2 %** (95 % CI: 12.8–35.6 %), **oligomenorrhoea 22. 7%** (95 % CI: 13.5–32.0 %), **polymenorrhea 16.2 %** (95 % CI: 10.7–21.6 %) and **abnormal cycle length 6.6%** (95 % CI: 5.0–8.2 %). The findings indicate that menorrhagia, oligomenorrhea, and polymenorrhea were the most common menstrual irregularities after vaccination, however, no strong conclusions about a causal relationship between COVID-19 vaccines and menstrual changes can be made from this.

Systematic review

A systematic review by Nazir et al. (TRIM D23-5442407) included review of 14 studies (3 cohort and 11 cross-sectional) involving a total of 78 138 vaccinated females. The various types of vaccines included in the studies were Sinopharm, Sinovac, CoVac, Modera, Astrazenica, Pfizer, CoronaVax, Novavax, and J & J/Janssen. Pooled data showed that just over half the women in the studies (52.05%, n =39 759) had some form of a menstrual problem after vaccination. Individual study results ranged from 0.83% to 90.9% of study participants reporting a menstrual abnormality. **Menorrhagia (heavy menstrual bleeding) was the most commonly observed adverse symptom of COVID-19 vaccines.**

Pre-test post-test quasi experiment evaluation

Bouchard et al. (TRIM D23-2002594) conducted a pretest–post-test quasi-experimental evaluation of menstrual cycle parameters before and after COVID-19 vaccination. Their study involved 76 menstruating individuals in North America who completed an online survey and monitored their menstrual cycles by either through cervical mucous observations or measuring urinary hormone levels using the ClearBlue Fertility Monitor. The data provided by the 76 participants looked at 227 pre-vaccine cycles, 145 vaccine cycles, 216 post-vaccine cycles. Whilst nearly a quarter (22%) of participants reported a subjective change in their menstrual cycle, there were **no significant differences in cycle length, length of menses**, estimated day of ovulation or luteal phase identified between the pre-vaccine, vaccine and post-vaccine cycles. This study was limited by a small sample size (authors noted that the study was under powered to detect changes in cycle length of <1 day), potential self-selection bias and only included menstruating individuals with regular cycles.

Population level cohort study

Trogstad et al. (pre-print) (TRIM D23-5497409) conducted a self-controlled case series using mobile-phone questionnaires in women aged 18-30 participating in the population-based Norwegian Young adult Cohort.

5,688 women were asked about their last menstrual cycle before COVID-19 vaccination and in the first 6 weeks following vaccination, including both first and second dose. 37.8% of participants reported any menstrual disturbance prior to vaccination.

The study found several menstrual disturbances that appeared to have a higher relative risk (RR) after first dose vaccination compared with prior to vaccination including **HMB** (RR 1.9 (95% CI 1.69-2.13), prolonged bleeding (RR 1.46, 95% CI 1.31-1.61), **short interval** (RR 1.32 95% CI 1.19-1.46), **spot bleeding** (RR 1.09 95% CI 1.01-1.17), with similar results after second dose with the addition of long interval now being statistically significant (RR 1.24, 95% CI 1.13-1.37).

This study calculates the prevalence and relative risk of several menstrual disturbances according to COVID-19 vaccination, showing that the prevalence of several disturbances appears to be higher after vaccination dose compared to prior vaccination. Among women who experienced disturbances after the first dose, almost two out of three women also experienced them after the second.

Cohort studies

Edelman *et al.* conducted a prospective cohort study in individuals using the "Natural cycles" menstrual cycle application. This cohort included US residents aged 18-45 years with normal cycles. The study look at menstrual cycle patterns in vaccinated individuals (3 cycles before the first COVID-19 vaccination and then 4-6 cycles following vaccine doses) and for unvaccinated individuals, 6 cycles over a similar time period. 3, 959 women were included in the study, of these 2403 were vaccinated and 1556 were unvaccinated. Vaccines included in the study were Pfizer, Moderna and Johnson & Johnson. Overall, COVID-19 vaccine was associated with a **less than 1-day change in cycle length** compared with pre-vaccine cycles and unvaccinated individuals saw no significant change. No change in menses length was found.

Eldelman *et al.* repeated their cohort study design as above, this time retrospectively looking at international users (UK, US, Canada, Europe) of the "Natural Cycles" application. This study involved 19,622 menstruating individuals (14 936 vaccinated, 4686 unvaccinated), and vaccines included were Pfizer, Moderna, AstraZeneca and Johnson & Johnson. Vaccinated individuals had a less than one day adjusted increase in length of their cycle. The adjusted difference was larger in people who received two doses of vaccine in a cycle. Changes resolved in the next cycle after vaccine receipt for those who received one dose in their cycle, but not yet for those who received two doses in their cycle. Changes in cycle length did not differ by vaccine type.

Gibson et al. (pre-print) (TRIM D23-5364006) conducted a longitudinal analysis of a subgroup of participants enrolled in the Apple Women's Health study that actively tracked their menstrual cycles. The cycles of a total of 9,652 participants (8,486 vaccinated; 1,166 unvaccinated) were analysed. Vaccines included Comirnaty, Spikevax and Johnson & Johnson vaccine. Among vaccinated participants, **COVID-19 vaccination was associated with a small increase in mean cycle length** (MCL) for cycles in which participants received the first dose (0.50 days, 95% CI: 0.22, 0.78) and cycles in which participants received the second dose (0.39 days, 95% CI: 0.11, 0.67) of mRNA vaccines compared with pre-vaccination cycles.

The study concluded that COVID-19 vaccination was associated with an immediate short-term increase in menstrual cycle length overall, however, the change was small and diminished in each cycle following vaccination.

Retrospective case-control study

Alvergne et al. (TRIM D23-5363994) conducted a secondary analysis on online survey data collected from 12, 579 vaccinated and unvaccinated individuals in the UK in 2021. They found that COVID-19 vaccination alone was not associated with changes to the

	menstrual cycle, however, a history of SARS CoV-2 infection was associated with abnormalities (HMB, missed periods and inter-menstrual bleeding). Analysis of VAERS adverse event reporting data Zhang et al. (TRIM D23-5282666) performed a stratified analysis of reports of menstrual disorders in the Vaccine adverse Event Reporting System (VAERS) from July 2, 1990 to November 12, 2021 and used the reporting odds ratio (ROR) to evaluate the relationship between COVID-19 vaccines and menstrual disorders. 13,118 (90.1%) of the 14,431 reports of menstrual disorders included in the study were related to COVID-19 vaccines. The ROR was 7.83 (95% confidence interval 7.39–8.28). The most commonly reported menstrual disorder was 'menstruation irregular'. Most reports were in females aged 30-49 years. The study concluded that: *"There is a potential safety signal when the COVID-19 vaccine is administered to young adult female (30–49 years old), resulting in menstrual disorders in. However, due to the well-known limitations of spontaneous reporting data, it is challenging to explicitly classify menstrual disorders as an adverse event of the COVID-19 Vaccines, and reports of adverse reactions to COVID-19 Vaccines in this age group should continue to be tracked."*
Biological plausibility	While a link between COVID-19 vaccines and menstrual cycle disorders has yet to be established, several plausible biological mechanisms have been postulated. Furthermore, menstrual irregularities have also been reported following SARS CoV-2 infection [4] suggesting that there could be a common trigger between natural infection and vaccination. As menstrual disorders have been reported across all COVID-19 vaccine platforms, it suggests that the mechanisms may be related to immunological responses rather than a specific vaccine component. Several menstrual disorders are related to disturbances in the hypothalamic-pituitary-ovarian axis (HPO axis) which can be caused by multiple different factors including stress, viral infections, and immunological influences. [5, 6] One theory is that vaccination could potentially trigger immunological responses that affect the HPO axis and hormones regulating the menstrual cycle. This theory is supported by menstruating individuals who are on hormonal contraceptives (and thus have stable levels of exogenous oestrogen and progesterone) being less likely to experience menstrual cycle irregularities following vaccination with a COVID-19 vaccine. The timing of vaccination during the menstrual cycle is also thought to potentially play a role, with the Apple Women's Health study finding that cycle length changes were only found when vaccination was given in the follicular phase of the menstrual cycle. [7] It has also been suggested that immune mediated effects following vaccination could also have effects on cells lining the uterus, [5] this could potentially explain unexpected bleeding during the menstrual cycle, HMB, prolonged bleeding and episodes of post-menopausal bleeding.

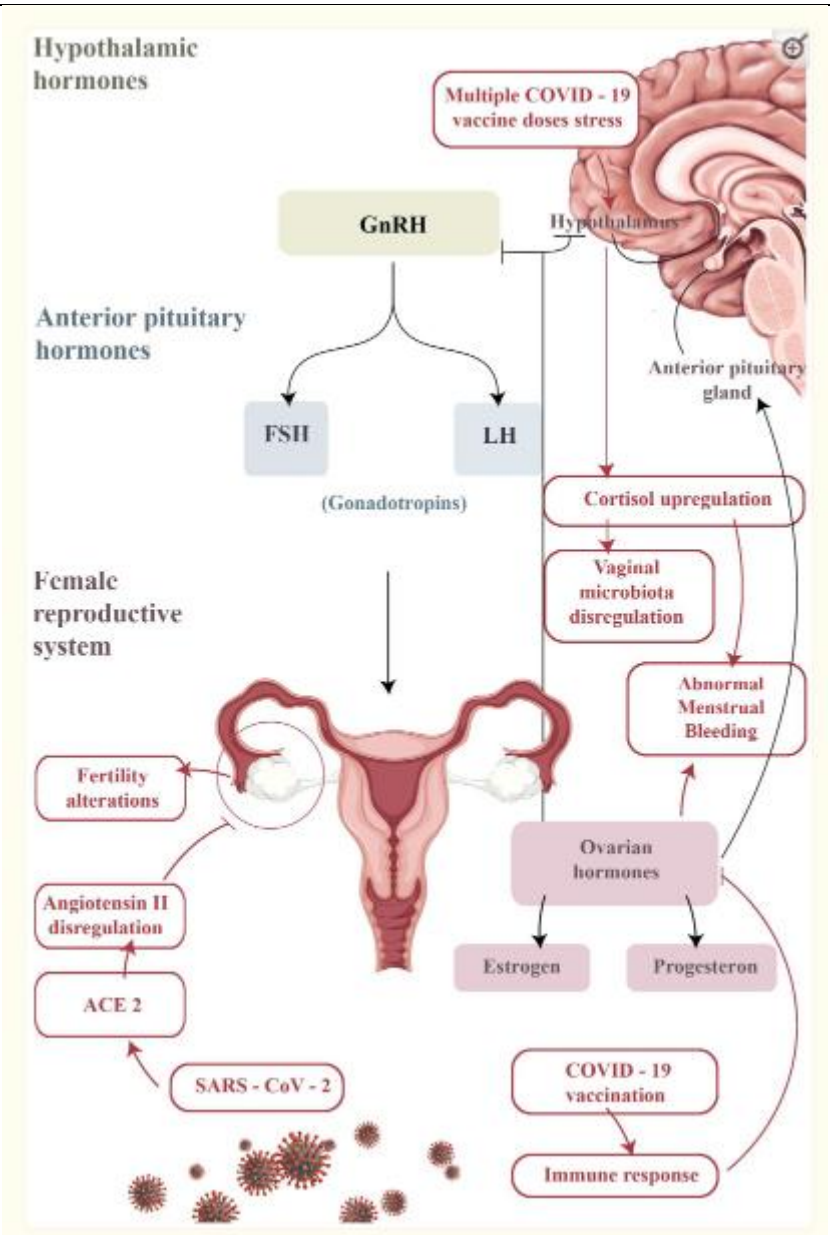

Image taken from: Dellino M et al. (TRIM D23-2053622)

Previous vaccines that have been reported to have an associated with menstrual abnormalities include the human papilloma virus (HPV) vaccine and Hepatitis B vaccine. [8-10] However, the evidence that either are associated with menstrual irregularities is very weak. For hepatitis B, there appears to be a single paper from 1982, reporting 7 out of 16 female hospital employees vaccinated with Hepatitis B vaccine experiencing menstrual abnormalities following vaccination. [8] The literature base related to HPV vaccine and menstrual abnormalities is also very small, with a study in Ngoya City involving nearly 30,000 participants not identifying an association, [9] and a recent systematic and meta-analysis published in January 2023 concluding that HPV vaccination does not seem to increase risk of primary ovarian insufficiency relative to unvaccinated people or other childhood vaccines.[10]

Impact on the Aboriginal and	Of the 2,934 AEFI reports of menstrual irregularities and COVID-19 vaccines, 56 reports (1.9%) were from individuals who identified as being Aboriginal and/or Torres Strait

Torres Strait Islander peoples	Islander. Based on the current data this does not suggest that Aboriginal and Torres Strait Islander people are disproportionately affected.

6. Conclusion

Conclusion	<Type here, then delete all italicised text below> *The conclusion should provide a clear rationale for the recommendation.*
Proposed action	☐**Refer to Stream B – MAVIS Evaluation Stream** ☒**Refer to Stream C – Regulatory Outcomes Stream (ROS)** ☐**Refer to <Other>** *(delete '<Other>', and specify which area, e.g. VERA)* ☐**Routine monitoring**
Instructions for Stream B, MAVIS Evaluation Stream (if applicable)	N/A
Instructions for Stream C, ROS (if applicable)	**Proposed regulatory action**

☐PI/CMI update	☐Recall
☐Safety alert	☐IPMST topic
☐Medicines Safety Update (MSU)	☐Pregnancy Category update
☐DHCP Letter	☐External/Internal liaison (specify)
☐RMP update	☒Other (specify) Sponsor signal assessment

Statement on validity/public health impact

Following the roll out of COVID-19 vaccines globally, there were numerous reports of menstrual cycle changes following vaccination through social media and also to adverse event reporting systems worldwide, with continued public and media interest in this topic.

Whilst the physical effects of menstrual disorders (excluding HMB) do not generally appear to be serious and are reported to be temporary in most cases, abnormalities in menstrual cycles can cause phycological distress and discomfort and can be of particular concern for individuals planning pregnancy or dealing with fertility issues. These concerns may also contribute to vaccine hesitancy.

Specific instructions for selected regulatory action(s)

Request sponsor of Comirnaty to undertake a signal assessment.

Instructions for <Other> (if applicable)	N/A

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Australian Government
Department of Health

Surveillance and Targeted Review Stream (STRS) – Targeted Investigation Process (TIP) for vaccines

Medicines and Vaccines Investigation and Surveillance Section

TRIM reference:
D21-3183500

Comirnaty (BNT162b2 [mRNA]) COVID-19 vaccine and Abortion spontaneous, Uterine contractions during pregnancy, Uterine contractions abnormal, Premature labour, Haemorrhage in pregnancy, Gestational hypertension, Foetal growth restriction, Foetal death, Abortion spontaneous incomplete (source extended SOC analysis)

Evaluator	EL1 Evaluator, Surveillance and Targeted Review Medicines and Vaccines Investigation Section
Date and Time completed	6/10/2021 4:30 PM

Summary

The vaccine event pair COMIRNATY (BNT162b2 [mRNA]) COVID-19 Vaccine Pfizer (PF) *and Abortion spontaneous, Uterine contractions during pregnancy, Uterine contractions abnormal, Premature labour, Haemorrhage in pregnancy, Gestational hypertension, Foetal growth restriction, Foetal death, Abortion spontaneous incomplete* was identified in an extended analysis of the MedDRA System Organ Class (SOC) *Pregnancy, puerperium and perinatal conditions* undertaken by Vaccine Epidemiology and Rapid Assessment Section and referred to Medicines and Vaccines Investigation Section for a Targeted Review on 13 September 2021. The Preferred Term (PT) Spontaneous abortion was identified as the main reason for the referral.

Spontaneous abortion, which is the loss of a pregnancy without outside intervention before 20 weeks gestation, affects up to 20 percent of recognized pregnancies. About 30 to 50 percentage of all pregnancies end prior to recognition. Spontaneous abortion can be subdivided into threatened abortion, inevitable abortion, incomplete abortion, missed abortion, septic abortion, complete abortion, and recurrent spontaneous abortion. Chromosomal abnormalities are causative in approximately 50 percent of spontaneous abortions; multiple other factors also may play a role including infection, improper implantation of fertilized egg in the uterine lining, certain medications, chronic conditions such as uncontrolled diabetes or thyroid disease.

Pregnant people are a priority group for COVID-19 vaccination and should be routinely offered an mRNA COVID-19 vaccine (Comirnaty – PF) or SPIKEVAX (elasomeran) COVID-19 VACCINE at any stage of pregnancy. mRNA vaccines (PF or Spikevax) are the preferred COVID-19 vaccines for people who are pregnant. Both PF and Spikevax are category B1 products in the Australian categorisation system and database for prescribing medicines in pregnancy. Pregnant women who cannot access an mRNA vaccine can consider vaccination with VAXZEVRIA ChAdOx1-S Z (AZ). AZ is a category B2 product.

There are 52 reports in the TGA's Adverse Events Management System (AEMS) related to PF and the MedDRA preferred terms (PTs) relating to abortion which include spontaneous abortion, missed abortion, incomplete spontaneous abortion and threatened abortion.

The reporting rate for Spontaneous Abortion is over double for AZ as compared to PF across females in the 20-29 and the 40-49 age groups and almost double for females in the 30-39 age group. The reason for this discrepancy in reporting rates is not clear and the numbers of reports are small. As pregnancy status is not recorded in the vaccine dosage data, these rates are derived from all females in the 20-49 years age group. The

MHRA however, has observed that the numbers of reports of miscarriage and stillbirth are low in relation to the number of pregnant women who have received COVID-19 vaccines to date.

The MedDRA Preferred Terms identified in an extended analysis of the MedDRA System Organ Class (SOC) *Pregnancy, puerperium and perinatal conditions* did not flag for PF or AZ in the March to June 2021 DPAR.

The Australian and other international product information (PI) for PF provide similar warnings on use during pregnancy, advising that 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. Administration of COMIRNATY in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and fetus.

The Australian, Canadian and United Kingdom national immunisation technical advisory groups (NITAGs) all preference the use of mRNA vaccines for people who are pregnant. The United States national advisory body, the Advisory Committee on Immunisation Practices (ACIP) advises that any of the currently FDA-approved or FDA-authorized COVID-19 vaccines can be administered to people in these groups and does not state a product preference. These NITAGs all agree that all pregnant women should receive COVID-19 vaccination at any stage of pregnancy. This is based on research that has shown that the risk of severe outcomes from COVID-19 is significantly higher for pregnant women and their unborn baby.

The Sponsor's (PF) Periodic Safety Update Report provides an update on *Special Patient Populations* which includes *Use in Pregnant/Lactating Women*. The update which includes information about the outcome of cases of pregnancy in the clinical studies, post authorisation data and a literature review concluded that no safety signals emerged from a review of these cases of use in pregnant/lactating women.

The MHRA's analysis of the safety of COVID-19 vaccines in pregnancy concludes that there is no pattern from the reports to suggest that any of the COVID-19 vaccines used in the UK, or any reactions to these vaccines, increase the risk of miscarriage or stillbirth.

The United States Centers for Disease Control (CDC) has established the v-safe COVID-19 Vaccine Pregnancy Registry to learn more about the safety of COVID-19 vaccines for people who are pregnant. The registry is collecting health information from people who received COVID-19 vaccination in the periconception period (within 30 days before last menstrual period) or during pregnancy. The initial report on the safety of mRNA COVID-19 vaccines administered during pregnancy based on analyses of data from three vaccine safety-related databases, including the v-safe pregnancy registry, did not identify any safety concerns for pregnant people who were vaccinated or for their babies.

The European Medicines Agency (EMA) has established the *COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER)* is to evaluate obstetric, neonatal, and infant outcomes among women vaccinated during pregnancy to prevent COVID-19. Data collection for this study commenced on 17/05/2021. The Final Report is due 30/04/2026.

The Public Health Agency of Canada is funding *Canadian COVID-19 Vaccines Registry for Pregnant and Lactating Individuals: An Evaluation of Safety, Effectiveness & Acceptability.* The purpose of this study is to collect data from pregnant, recently pregnant, and lactating women & individuals, regardless of whether they have received a COVID-19 vaccine, to assess the safety and effectiveness of COVID-19 vaccines and to examine attitudes towards COVID-19 vaccination in this population. Dates for publication of data from the registry are not available.

A literature search identified preliminary findings from the US v-safe registry which did not identify obvious safety signals among pregnant persons who received mRNA Covid-19 vaccines. However, more longitudinal follow-up, including follow-up of large numbers of women vaccinated earlier in pregnancy, is necessary to inform maternal, pregnancy, and infant outcomes. A study of COVID-19 infection and pregnancy demonstrated a consistent association between pregnant individuals with COVID-19 diagnosis and higher rates of adverse outcomes, including maternal mortality, preeclampsia, and preterm birth compared with pregnant individuals without COVID-19 diagnosis.

It is the conclusion of this review that based on the current information there is insufficient evidence to suggest that vaccination with PF is harmful for pregnant women or their babies. However, more information about the safety of mRNA vaccines for pregnant women and their babies will become available as more

longitudinal follow-up is completed, including follow-up of large numbers of women vaccinated earlier in pregnancy. The initial signal of a possible higher rate of spontaneous abortion among PF vaccine recipients compared to AZ vaccine recipients was not verified in this review.
Recommendations
It is recommendation of this review to continue to monitor reports of pregnancy and foetal related adverse events following vaccination with COVID-19 vaccines through routine pharmacovigilance process including environmental scanning of published literature and monitoring the findings from the COVID-19 vaccine pregnancy registers that have been established in the United States, Canada and Europe.
Priority
High
Delegate's Comment
The delegate endorses the recommendations outlined above (unchanged).

DISCLAIMER: The purpose of this report is to provide a targeted assessment (at a point in time) of the described vaccine-event pair to assist with triage of workflow. It does not constitute a full evaluation nor a regulatory decision.

1. List of abbreviations

Abbreviation	Meaning
ACCESS	Australia-Canada-Singapore-Switzerland-United Kingdom (consortium)
ADR/AE	Adverse Drug Reaction / Adverse Event
AEFI	Adverse Event Following Immunisation
AEMS	Adverse Event Management System
AESI	Adverse Event of Special Interest
AIR	Australian Immunisation Register
ARTG	Australian Register of Therapeutic Goods
ATAGI	Australian Technical Advisory Group on Immunisation
ATC	Anatomical Therapeutic Chemical (classification system)
AZ	VAXZEVRIA ChAdOx1-S, previously COVID-19 Vaccine AstraZeneca
CMI	Consumer Medicine Information
COVID-19	Coronavirus disease 2019
DHCPL	Dear Healthcare Professional Letter
EMA	European Medicines Agency (European Union)
FDA	Food and Drug Administration (United States)
GACVS	Global Advisory Committee on Vaccine Safety
IC	Information Component
ICMRA	International Coalition of Medicines Regulatory Authorities
IPMST	International Post Market Surveillance Teleconference
MaVIS	Medicines and Vaccines Investigation and Surveillance
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency (United Kingdom)
MSSR	Monthly Safety Summary Report
MSU	Medicines Safety Update
NCIRS	National Centre for Immunisation Research and Surveillance
O/E	Observed vs. Expected (analysis)

PF	COMIRNATY (BNT162b2 [mRNA]) COVID-19 Vaccine Pfizer
PI	Product Information
PRAC	Pharmacovigilance Risk Assessment Committee
PRR	Proportional Reporting Ratio
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
RMP	Risk Management Plan
ROS	Regulatory Outcomes Stream
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SPC/SmPC	Summary of Product Characteristics
STRS	Surveillance and Targeted Review Stream
TIP	Targeted Investigation Process
VERA	Vaccine Epidemiology and Rapid Action
VSIG	Vaccine Safety Investigation Group
WHO-UMC	World Health Organisation – Uppsala Monitoring Centre

DELETE: Please list all the abbreviations used in your report in the table provided above. Some examples have been included in the table.

2. Vaccine information

Indication(s)	COMIRNATY (BNT162b2 [mRNA]) COVID-19 Vaccine Pfizer (PF): Provisional approval for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older.
Vaccine roll-out status	All people aged 12 years to 59 years are able to book an appointment for PF. You should not receive this vaccine if you have had: • anaphylaxis (a type of severe allergic reaction) to a previous dose of an mRNA COVID19 vaccine (i.e., Pfizer or Spikevax) • anaphylaxis after exposure to any component of the vaccine, including polyethylene glycol (PEG) • myocarditis and/or pericarditis attributed to a previous dose of an mRNA COVID-19 vaccine (i.e., Pfizer or Spikevax) • any other serious adverse event, that following review by an experienced immunisation provider or medical specialist was attributed to a previous dose of an mRNA COVID-19 vaccine (i.e., Pfizer or Spikevax) and without another cause identified PF is preferred over VAXZEVRIA ChAdOx1-S, previously COVID-19 Vaccine AstraZeneca (AZ) in people aged < 60 years. This is based on the higher risk and observed severity of thrombosis and thrombocytopenia syndrome (TTS) in people < 60 years compared to those ≥ 60. However, AZ can be used in adults aged < 60 years if PF if the person has made an informed decision based on an

	understanding of the risks and benefits. In outbreak settings, adults <60 years of age should strongly consider AZ if they are unable to access PF. The Department of Health has published guidance: *COVID-19 vaccination decision guide for women who are pregnant, breastfeeding or planning pregnancy version 6 - updated on15 September 2021.* [TRIM D21-3140558] This decision guide contains information about Pfizer and Spikevax, the COVID-19 vaccines recommended if you are pregnant, breastfeeding or planning pregnancy. This guide will be updated as new information becomes available. Key points include: • If you are pregnant you are a priority for COVID-19 vaccination and should be routinely offered Pfizer or Spikevax at any stage of pregnancy. • If you are trying to become pregnant, you do not need to delay vaccination or avoid becoming pregnant after vaccination. • Real-world evidence has shown that Pfizer and Spikevax are safe if you are pregnant and breastfeeding. • AstraZeneca can be considered if you are pregnant, breastfeeding or planning pregnancy, if you cannot access Pfizer or Spikevax, and if the benefits of vaccination outweigh the risks for you. • If you are pregnant, you have a higher risk of severe illness from COVID-19. • Your baby may also have a higher risk of being born prematurely. • COVID-19 vaccination may provide indirect protection to babies by transferring antibodies through the placenta (during pregnancy) or through breastmilk (during breastfeeding).
Mechanism of action	The nucleoside-modified messenger RNA in COMIRNATY is formulated in lipid nanoparticles, which enable delivery of the non-replicating RNA into host cells to direct transient expression of the SARS-CoV-2 spike (S) antigen. The mRNA codes for membrane-anchored, full-length S with two-point mutations within the central helix. Mutation of these two amino acids to proline locks S in an antigenically preferred prefusion conformation. COMIRNATY elicits both neutralising antibody and cellular immune responses to the antigen, which may contribute to protection against COVID-19.

3. Adverse event information

Signal Source	The vaccine event pair PF *and Abortion spontaneous, Uterine contractions during pregnancy, Uterine contractions abnormal, Premature labour, Haemorrhage in pregnancy, Gestational hypertension, Foetal growth restriction, Foetal death, Abortion spontaneous incomplete* was identified in an extended analysis of the MedDRA System Organ Class (SOC) *Pregnancy, puerperium and perinatal conditions* undertaken by Vaccine Epidemiology and Rapid Assessment Section and referred to Medicines and Vaccines Investigation Section for a Targeted Review on 13 September 2021. The Preferred Term (PT) Spontaneous abortion was identified as the main reason for the referral. This analysis showed a higher reporting rate for the PF vaccine compared to the AZ vaccine, when all PTs in the SOC were combined. [TRIM D21-3087734]
AESI status	Pregnancy and birth outcomes are listed as a Category 4 outcome. They were added to the AESI list by the TGA following clinical evaluation and the potential for COVID-19 vaccines to be administered to pregnant women as off-label usage. Pregnant people are a priority group for COVID-19 vaccination and should be routinely offered an mRNA COVID-19 vaccine (Comirnaty or Spikevax) at any stage of pregnancy. mRNA vaccines (Comirnaty or Spikevax) are the preferred COVID-19 vaccines for people who are pregnant. Pregnant women who cannot access an mRNA vaccine can consider vaccination with AZ. Both PF and Spikevax are category B1 products in the Australian

<table>
<tr><td></td><td>categorisation system and database for prescribing medicines in pregnancy as there is limited experience with their use in pregnant women. A combined fertility and development toxicity study in rats did not show vaccine-related harmful effects on embryofetal development.

AZ is a category B2 product as there are a limited amount of data from use in pregnant women, or women who became pregnant after receiving the vaccine. The data are insufficient to inform on vaccine associated risk. Animal reproductive toxicity studies have not been completed.

The current advice to pregnant women for all three vaccines is intentional off-label usage and requires close monitoring.

The current AESI list for COVID-19 is located at TRIM D20-3595626.</td></tr>
<tr><td>AEFI</td><td>Spontaneous abortion, which is the loss of a pregnancy without outside intervention before 20 weeks' gestation, affects up to 20 percent of recognized pregnancies. About 30 to 50 percentage of all pregnancies end prior to recognition. Spontaneous abortion can be subdivided into threatened abortion, inevitable abortion, incomplete abortion, missed abortion, septic abortion, complete abortion, and recurrent spontaneous abortion. Chromosomal abnormalities are causative in approximately 50 percent of spontaneous abortions; multiple other factors also may play a role including infection, improper implantation of fertilized egg in the uterine lining, certain medications, chronic conditions such as uncontrolled diabetes or thyroid disease.</td></tr>
<tr><td>Magnitude of signal</td><td>TGA DPAR
The MedDRA preferred terms (PTs) Abortion spontaneous, Uterine contractions during pregnancy, Uterine contractions abnormal, Premature labour, Haemorrhage in pregnancy, Gestational hypertension, Foetal growth restriction, Foetal death, Abortion spontaneous incomplete identified in an extended analysis of the MedDRA System Organ Class (SOC) Pregnancy, puerperium and perinatal conditions did not flag for PF or AZ in the March to June 2021 DPAR. [TRIM D21-2947984]

Reporting Rates

A comparison of the TGA reporting rates by age groups between PF and AZ for the Spontaneous Abortion and related PT'*s to describe miscarriage up to and including 29 September 2021.

<table>
<tr><td>Age</td><td>20-29</td><td>30-39</td><td>40-49</td></tr>
<tr><td colspan="4">PF</td></tr>
<tr><td>Doses for females</td><td>1515832</td><td>1920929</td><td>2184540</td></tr>
<tr><td>Reports</td><td>5</td><td>38</td><td>4</td></tr>
<tr><td>Reporting Rate per 100,000 doses</td><td>0.33</td><td>1.98</td><td>0.18</td></tr>
<tr><td colspan="4">AZ</td></tr>
<tr><td>Doses for females</td><td>255336</td><td>268013</td><td>198659</td></tr>
<tr><td>Reports</td><td>2</td><td>10</td><td>1</td></tr>
<tr><td>Reporting Rate per 100,000 doses</td><td>0.78</td><td>3.73</td><td>0.50</td></tr>
</table>
*spontaneous abortion, missed abortion, incomplete spontaneous abortion, threatened abortion

Note – Two PF case reports did not provide the age of the patient and are not included on the table.

The reporting rate for Spontaneous Abortion is over double for AZ as compared to PF across the 20-29 and the 40-49 age groups and almost double for the 30-39</td></tr>
</table>

	age group. The reason for this discrepancy in reporting rates is not clear and the numbers of reports are small. The accuracy of the calculated reporting rate is impacted several considerations including: • Australian Immunisation register which is used to calculate dosage numbers does not identify people who are pregnant, so the exposure to the vaccine is based on all females between the ages of 20-49 years • At in at least eight of the 52 cases reports related to abortion and PF, the reporter identified that they were unaware of their pregnancy at the time of vaccination. • Early onset spontaneous abortion is often under identified and consequently under reported. There have been no reports for the PT's identified in the *Pregnancy, puerperium and perinatal conditions* (SOC)for Spikevax at this time. This finding is not unexpected as Spikevax has just been introduced to the COVID-19 vaccination roll out. The dose numbers for females for AZ and PF up to an including 29/09/2021 were obtained via QLIK on 30/09/2021. [TRIM D21-3158431]. The number of case reports were identified in a QLIK search undertaken on 30/09/2021. The PCDs for PF are filed in TRIM: D21-3158457. The PCDs for AZ are filed in TRIM: D21-3158460.
No. of AEFI reports	**PF Vaccine** A QLIK search was undertaken on 5/10/2021 using the default bookmark, the tradename PF and the *Pregnancy, puerperium and perinatal conditions* SOC. This search identified 62 case reports. The Preferred terms (PTs) reported included*: 49 reports of spontaneous abortion, 2 reports of gestational hypertension, 2 reports of Haemorrhage in pregnancy and a single report of each of the following: missed abortion, incomplete spontaneous abortion, threatened abortion, ectopic pregnancy, foetal death, foetal growth restriction, foetal hypokinesia, morning sickness, premature delivery, premature labour, abnormal uterine contractions, and uterine contractions during pregnancy. The PCDs for the 62 reports are filed in TRIM. [D21-3174568] *Note that more than one PT can be included in each case report. In terms of age group, 90% (56 cases) are in the 18-44 age group, 6.5% (4 cases) are in the 45-64 age group and for 3.5% (2 cases) the age was not provided in the report. In terms of doses, of the 62 case reports, 35.5% (22 cases) were reported following dose one, 40.3% (25 cases) were reported following dose two and 24.2% (15 cases) did not report the dose information. The management of the events reports: • 15 cases reported management by a GP • 11 cases reported management in a hospital ED • 8 cases reported a hospital admission • 2 case reports reported self • 4 case reports reported unknown • 22 case reports did not complete this field. The outcome of the reaction reported: • 13 cases were reported as not recovered / not resolved / ongoing • 15 cases were reported as recovered / resolved • 3 cases were reported as recovered / resolved with sequelae • 6 cases were reported as recovering / resolving

	• 25 cases the outcome was reported as unknown. There were no fatal outcomes reported. **AZ Vaccine** A QLIK search was undertaken on 5/10/2021 using the default bookmark, the tradename AZ and the *Pregnancy, puerperium and perinatal conditions* SOC. This search identified 13 case reports. The Preferred terms (PTs) reported were*: 13 reports of spontaneous abortion and 1 report of Ectopic pregnancy with contraceptive device. The PCDs for the 13 reports are filed in TRIM. [D21-3174624] *Note that more than one PT can be included in each case report. In terms of age group, all of the 13 cases are in the 18-44 age group. In terms of doses, of the 13 case reports, 77% (10 case reports) were reported following dose one and 23% (3 case reports) were reported following dose two. The management of the events reports: • 4 cases reported management by a GP • 5 cases reported management in a hospital ED • 4 case reports did not complete this field. The outcome of the reaction reported: • 2 cases were reported as not recovered / not resolved / ongoing • 3 cases were reported as recovered / resolved • 1 cases were reported as recovering / resolving • 7 cases the outcome was reported as unknown. There were no fatal outcomes reported.
Summary of AEFI reports	A high-level review of the Case reports in the TGA's Adverse Events Management System was conducted focusing PF and the PTs relating to Abortion: • spontaneous abortion • missed abortion • incomplete spontaneous abortion • threatened abortion. This identified 52 case reports. Of the 52 case reports, eight cases reported that they were unaware of their pregnancy at the time of vaccination. 13 cases reported provided no narrative or times to onset of the AEFI reported. Most of the case reports related to pregnancy prior to 12 weeks. Several reporters stated that they didn't think that the AEFI was related to the vaccine but submitted a report as it was new vaccine. The AEFI reports demonstrate the temporal relation of spontaneous abortion and the administration of PF. However, given the high rate for spontaneous abortion which ranges from an estimated 1 in 3 to 1 in 5 of all pregnancies it is difficult to assess causality.

4. Regulatory surveillance

Local, including: **PI, Sponsor's PSUR/MSSR, and applicable clinical guidance**	**Product Information (PI)**
	The Australian Product Information for Comirnaty version: pfpcovii20921 was revised on 21 September 2021. [TRIM **Section 4.6 Fertility, pregnancy and lactation** **Effects on fertility** In a combined fertility and developmental toxicity study, female rats were intramuscularly administered COMIRNATY prior to mating and during gestation (4 full human doses of 30 µg each, spanning between pre-mating day 21 and gestation day 20). SARS CoV-2 neutralising antibodies were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well

as in fetuses and offspring. There were no vaccine related effects on female fertility and pregnancy rate**.**

Use in pregnancy - Pregnancy Category B1*
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 Effects on fertility). Administration of COMIRNATY in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and fetus.
***** The Australian categorisation system and database for prescribing medicines in pregnancy have been developed by medical and scientific experts based on available evidence of risks associated with taking particular medicines while pregnant. [1]**Category B1:** Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

Use in lactation
It is unknown whether BNT162b2 [mRNA] is excreted in human milk. A combined fertility and developmental toxicity study in rats did not show harmful effects on offspring development before weaning (see Effects on fertility).

Applicable clinical guidance

The Australian Technical Advisory Group on Immunisation (ATAGI) Clinical guidance on use of COVID-19 vaccine in Australia in 2021 (v7.2) was last updated on 23 September 2021. [TRIM D21-3158480]

Women and adolescents ≥ 12 years who are pregnant, breastfeeding or planning pregnancy

Pregnant people are a priority group for COVID-19 vaccination and should be routinely offered an mRNA COVID-19 vaccine (Comirnaty or Spikevax) at any stage of pregnancy. mRNA vaccines (Comirnaty or Spikevax) are the preferred COVID-19 vaccines for people who are pregnant. This is based on the growing body of evidence supporting the safety of mRNA vaccines in pregnancy, while there are still very limited data on the safety of viral vector vaccines (such as COVID-19 Vaccine AstraZeneca) in pregnancy. However pregnant women who cannot access an mRNA vaccine can consider vaccination with COVID-19 Vaccine AstraZeneca if the benefits to the individual outweigh the potential risks. Pregnant women who received a first dose of COVID-19 Vaccine AstraZeneca can receive either an mRNA COVID-19 vaccine (Comirnaty or Spikevax) or COVID-19 Vaccine AstraZeneca for their second dose, although an mRNA vaccine is preferred.

Women who are breastfeeding or planning pregnancy are preferred to have an mRNA COVID-19 vaccine because of their age (i.e. mRNA vaccines are the preferred vaccines for all people under 60) and because post marketing studies demonstrate safety of these vaccines in pregnancy. However, there are no theoretical safety concerns associated with the use of COVID-19 Vaccine AstraZeneca specific to breastfeeding or planning pregnancy, and women in these groups who cannot access an mRNA COVID-19 vaccine should consider vaccination with COVID-19 Vaccine AstraZeneca, particularly in outbreak settings.

Pregnant women with COVID-19 have a higher risk of intensive care admission (OR 2.13, 95% CI 1.53 - 2.95), invasive ventilation (2.59, 95% CI 2.28 - 2.94), need for extra corporeal membrane oxygenation (OR 2.02, 95% CI 1.22 - 3.34) and preterm birth (OR 1.47, 95% CI 1.14 – 1.91) compared with non-pregnant

[1] Prescribing medicines in pregnancy database accessed 27 September 2021. https://www.tga.gov.au/prescribing-medicines-pregnancy-database

reproductive aged women20 with COVID-19. Factors which increase the risk of severe illness and death from COVID-19 during pregnancy include increased maternal age, high body mass index and pre-existing co-morbidities. Infants born to mothers with COVID-19 are more likely to require admission to the neonatal intensive care unit (OR 4.89, 95% CI 1.87 – 12.81) versus those without COVID-19.

In a prospective cohort study of over 35,000 pregnant women who received an mRNA COVID-19 vaccine (54% received Comirnaty, 46% received Spikevax), the adverse event profile was similar to that of non-pregnant women. Pregnant women were slightly more likely to report injection site pain, and less likely to report generalised symptoms such as fever or tiredness. Fever of 38°C or above was reported by fewer than 1% of pregnant women after the first dose of Comirnaty or Spikevax, and fewer than 5% after the second dose of Comirnaty, and 11.8% after the second dose of Spikevax. Fever of 39°C occurred in < 0.05% of pregnant participants after the first dose, and 0.5% after the second dose. The findings from this large study are supported by other smaller observational studies.

The same study reported on pregnancy and neonatal outcomes in 827 women who received an mRNA COVID19 vaccine in pregnancy, and did not identify any safety concerns. Complications such as preterm delivery, stillbirth, small for gestational age infants and congenital anomalies occurred at a similar rate to what is seen in the general population. In the clinical trial for Comirnaty, 23 women became pregnant during the study period, of which 11 had received Comirnaty. In the clinical trial for Spikevax,13 individuals were unknowingly pregnant or became pregnant during the trial, of which six received the vaccine. Information about the outcomes of their pregnancies is awaited. A phase 2/3 randomised controlled trial of Comirnaty in pregnant women is underway in the US.

A more recent (pre-print) study reported on this same cohort with updated data investigated 2456 women vaccinated with at least one dose of Comirnaty (53%) or Spikevax (47%) in the preconception period (up to 30 days prior to the first day of the last menstrual period) or during pregnancy before 20 weeks' gestation. It found the age-standardised cumulative risk of spontaneous abortion occurring at 6 to 19 weeks of gestation was 12.8% (95% CI: 10.8 to 14.8%). This rate was within the expected range of the reported background rate in high income countries. The highest risk of spontaneous abortion was observed in weeks 8 and 9 of gestation, and this risk decreased markedly after week 13 of gestation, comparable to what is observed in the general population.

Animal studies of Comirnaty and Spikevax have not shown any negative effects on fertility or pregnancy. In humans, two studies have evaluated assisted reproductive therapy (ART) outcomes in the same couples before and after Comirnaty.5758 Two other studies compared ART outcomes among those vaccinated with an mRNA COVID-19 vaccine, those previously infected with SARS-CoV-2 and those neither infected nor vaccinated. No adverse effects of vaccination on oocyte quality and retrieval, fertilisation rates, top-quality embryo rates, and sustained implantation rates were observed.

Evidence of vaccine effectiveness of mRNA COVID-19 vaccines in pregnant women is also emerging. A retrospective cohort study that included 15,060 pregnant women in Israel, including 7,530 who received Comirnaty, estimated effectiveness against PCR-confirmed SARS-CoV-2 infection from ≥ 28 days post vaccination to be 78% (95% CI 57 to -89%).

Sponsor's PSUR/MSSR

The Sponsor's Monthly Summary Safety Report (MSSR) for PF covering the period 01 August through 31 August 2021 was submitted to the TGA on 14 September 2021. [TRIM D21-3103755]

	The Internal review of cases indicative of drug exposure during pregnancy for the reporting period included in the MSSR, did not reveal any new safety information. Whether the frequency of pregnancy outcomes, pregnancy related events, and newborn events is consistent with expectation cannot be evaluated based on the spontaneous reports. The number of pregnant women who have received the COVID-19 vaccine is unknown. The MAH is conducting study C4591015 to study the safety of Comirnaty in pregnant women - this study is conducted as a committed Post-Authorization Safety Study. Other Post-Authorization Safety Studies planned or being conducted may inform regarding pregnancy. The Sponsor's first Periodic Safety Update (PSUR) for PF covering the period 19 December 2020 through 18 June 2021 was submitted to the TGA on 19 August 2021. [TRIM D21-3029287] The PSUR provides an update on *Special Patient Populations* which includes *Use in Pregnant/Lactating Women*. The update which includes information about the outcome of cases of pregnancy in the clinical studies, post authorisation data and a literature review concluded that no safety signals emerged from a review of these cases of use in pregnant/lactating women.
US FDA	**Label** The Pfizer-Biontech COVID-19 Vaccine Fact Sheet and label for Health Care Providers was last updated on 22 September 2021. [TRIM D21-3148988] Section 11 *Use in Specific Populations* in the Fact Sheet provides risk summaries about: • 11.1 *Pregnancy* 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. • 11.2 *Lactation* Data are not available to assess the effects of Pfizer-BioNTech COVID-19 Vaccine on the breastfed infant or on milk production/excretion. The Comirnaty (Covid-19 Vaccine, mrna) and Pfizer-Biontech Covid-19 Vaccine Factsheet for recipients and caregivers provides advice for recipients to inform the vaccination provider if they are pregnant or plan to become pregnant prior to vaccination. It also advises potential recipients who are pregnant or breast feeding to discuss their options with their healthcare provider prior to vaccination. **Advisory Committee on Immunisation Practices (ACIP) CDC** The Advisory Committee on Immunisation Practices (ACIP) Centres for Disease Control and Prevention (CDC) *Interim Clinical Considerations for Use of COVID-19*

	Vaccines Currently Approved or Authorized in the United States was last updated on 27 September 2021. [TRIM D21-3150370]. The considerations involving pregnancy, lactation and fertility recommend COVID-19 vaccination for all people aged 12 years and older, including people who are pregnant, lactating, trying to get pregnant now, or might become pregnant in the future. Any of the currently FDA-approved or FDA-authorized COVID-19 vaccines can be administered to people in these groups; ACIP does not state a product preference. However, all women aged <50 years should be aware of the rare risk of TTS after receipt of the Janssen COVID-19 vaccine and the availability of other currently FDA-approved or FDA-authorized COVID-19 vaccines (i.e., mRNA vaccines) for which this risk has not been seen. There is no evidence that any of the COVID-19 vaccines affect current or future fertility. The CDC established the v-safe COVID-19 Vaccine Pregnancy Registry to learn more about the safety of COVID-19 vaccines for people who are pregnant. The registry is collecting health information from people who received COVID-19 vaccination in the periconception period (within 30 days before last menstrual period) or during pregnancy. The information is critical to helping people and their healthcare providers make informed decisions about COVID-19 vaccination. Participation is voluntary, and participants may opt out at any time. v-safe is a smartphone-based tool that uses text messaging and web surveys to provide personalized health check-ins after you receive a COVID-19 vaccine. The v-safe COVID-19 Vaccine Pregnancy Registry is for v-safe participants who self-identify as pregnant at the time of vaccination or shortly thereafter (within 30 days of vaccination). The registry activities are in addition to the v-safe after vaccination health check-ins that participants receive via text message. Pregnant participants in the registry will be contacted to answer questions about their pregnancy and medical history. Participants will also be asked for permission to contact their healthcare provider(s). [TRIM D21-3150320] CDC released the first U.S. data on the safety of mRNA COVID-19 vaccines administered during pregnancy based on analyses of data from three vaccine safety-related databases, including the v-safe pregnancy registry. The analyses did not identify any safety concerns for pregnant people who were vaccinated or for their babies. [TRIM D21-3150281]
EU EMA	**Summary of Product Characteristics (SmPC)** The European Medicines Agency (EMA) Comirnaty Summary of Product Characteristics (SmPC) was last updated on 24 September 2021. [TRIM D21-3150580] Section 4.6 of the SmPC provides the following information about Pregnancy, Breast Feeding and Fertility: 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/foetal development, parturition or post-natal development (see section 5.3). Administration of Comirnaty in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus. Breast-feeding - It is unknown whether Comirnaty is excreted in human milk. Fertility - Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Section 5.3 –Reproductive and developmental toxicity were investigated in rats in a combined fertility and developmental toxicity study where female rats were intramuscularly administered Comirnaty prior to mating and during gestation (receiving 4 full human doses that generate relatively higher levels in rat due to body weight differences, spanning between pre-mating day 21 and gestational day 20). SARS-CoV-2 neutralizing antibody responses were present in maternal

	animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk. The EMA is coordinating observational studies in EU Member States looking at real-world data from clinical practice to monitor the safety and effectiveness of COVID-19 vaccines, including in pregnant women. The objective of the *COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER)* is to evaluate obstetric, neonatal, and infant outcomes among women vaccinated during pregnancy to prevent COVID-19. Specifically, the C-VIPER will estimate the risk of obstetric outcomes (abortion, antenatal bleeding, dysfunctional labor, gestational diabetes, hypertensive disorders of pregnancy, intrauterine growth retardation, maternal death, non-reassuring fetal status, pathways to premature birth, postpartum hemorrhage, and COVID-19), neonatal outcomes (congenital anomalies, failure to thrive, low birth weight, neonatal death, neonatal encephalopathy, neonatal infections, preterm birth, respiratory distress in the newborn, small for gestational age, stillbirth, and COVID-19), and infant outcomes (height, weight, health conditions, developmental milestones until one year of age, and COVID-19) among pregnant women exposed to a COVID-19 vaccine from 30 days prior to the first day of the last menstrual period to end of pregnancy and their offspring relative to a matched unexposed reference group. Data collect ion for this study commenced on 17/05/2021. The Final Report is due 30/04/2026.
	Pharmacovigilance Risk Assessment Committee (PRAC)
	N/A
UK MHRA	**Summary of Product Characteristics (SPC)**
	The Comirnaty Summary of Product Characteristics (SPC) was last updated on 11 August 2021. [TRIM D21-3151671] Section 4.6 of the SPC addresses Fertility, Pregnancy and Lactation: 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/foetal development, parturition or post-natal development (see section 5.3). Administration of Comirnaty in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus. Breast-feeding - It is unknown whether Comirnaty is excreted in human milk. Fertility - Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3) Section 5.3 - Reproductive toxicity - Reproductive and developmental toxicity were investigated in rats in a combined fertility and developmental toxicity study where female rats were intramuscularly administered Comirnaty prior to mating and during gestation (receiving 4 full human doses that generate relatively higher levels in rat due to body weight differences, spanning between pre-mating day 21 and gestational day 20). SARS-CoV-2 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No Comirnaty data are available on vaccine placental transfer or excretion in milk.
	Yellow Card reporting / Relevant regulatory action
	The current *Coronavirus vaccine – weekly summary of Yellow Card reporting* covers the period 9 December 2020 to 15 September 2021 and was updated on 23 September 2021. [TRIM D21-3152168]

	The Summary includes a section about the safety of COVID-19 vaccines in pregnant and breastfeeding women. Safety of COVID-19 vaccines in pregnancy - The MHRA closely monitors the safety of COVID-19 vaccine exposures in pregnancy, including Yellow Card reports for COVID-19 vaccines used in pregnancy. These reports have been reviewed by the independent experts of the Commission on Human Medicines' COVID-19 Vaccines Benefit Risk Expert Working Group and by the Medicines for Women's Health Expert Advisory Group (MWHEAG). Pregnant women have the same risk of getting COVID-19 as non-pregnant women but they may be at an increased risk of becoming severely ill, particularly if they get infected in the third trimester or if they also have underlying medical problems, compared to non-pregnant women. **The current advice of the Joint Committee on Vaccination and Immunisation (JCVI) is that the COVID-19 vaccines should be offered to those who are pregnant at the same time as non-pregnant individuals based on their age and clinical risk group. The Pfizer/BioNTech and Moderna vaccines are currently the preferred vaccines for use during pregnancy**. The numbers of reports of miscarriage and stillbirth are low in relation to the number of pregnant women who have received COVID-19 vaccines to date (more than 72,000) and how commonly these events occur in the UK outside of the pandemic. There is no pattern from the reports to suggest that any of the COVID-19 vaccines used in the UK, or any reactions to these vaccines, increase the risk of miscarriage or stillbirth. **Sadly, miscarriage is estimated to occur in about 20 to 25 in 100 pregnancies in the UK and most occur in the first 12 to 13 weeks of pregnancy (the first trimester). Stillbirths are sadly estimated to occur in about 1 in 200 pregnancies in the UK.** A few reports of commonly occurring congenital anomalies and preterm births have also been received. There is no pattern from the reports to suggest that any of the COVID-19 vaccines used in the UK increase the risk of congenital anomalies or birth complications. Pregnant women have reported similar suspected reactions to the vaccines as people who are not pregnant. Like most vaccines and medicines, clinical trials of COVID-19 vaccine in pregnant women were not carried out prior to use of the vaccines in the general population. However, evidence from non-clinical studies of the COVID-19 vaccines available in the UK have not raised any concerns about safety in pregnancy. The COVID-19 vaccines do not contain organisms that can multiply in the body, so they cannot infect an unborn baby in the womb. Extensive international experience for the Pfizer/BioNTech Vaccine and COVID-19 Vaccine Moderna used in pregnancy have also not raised any safety concerns. The MHRA will continue to closely monitor safety data for use of the COVID-19 vaccines in pregnancy, including through evaluation of electronic healthcare record data. Safety of COVID-19 vaccines in breastfeeding - The MHRA closely monitors the safety of COVID-19 vaccines during breastfeeding, including evaluation of Yellow Card reports for COVID-19 vaccines from breastfeeding women. These reports have been reviewed by the independent experts of the Commission on Human Medicines' COVID-19 Vaccines Benefit Risk Expert Working Group, by paediatric and breastfeeding experts. There is no current evidence that COVID-19 vaccination while breastfeeding causes any harm to breastfed children or affects the ability to breastfeed. COVID-19 vaccines do not contain live components and there is no known risk associated with being given a non-live vaccine whilst breastfeeding. The current advice of the Joint Committee on Vaccination and Immunisation (JCVI) is that

	breastfeeding parents may be offered any suitable COVID-19 vaccine depending on their age. We have received about 3,000 Yellow card reports from women breastfeeding at the time of vaccination. Most of these women reported only suspected reactions in themselves which were similar to reports for the general population, with no effects reported on their milk supply or in their breastfed children. A small number of women have reported decreases in their milk supply, most of which were transient, or possible reactions in their breastfed child. A number of factors can affect milk supply and infant behaviour, including general maternal health, amount of sleep, and anxiety. The symptoms reported for the children (high temperature, rash, diarrhoea, vomiting and general irritability) are common conditions in children of this age, so some of the effects reported may have occurred by coincidence. A small number of women may experience a reduction in their breast milk production and it may be helpful for breastfeeding women to know how to maintain their breast milk supply, particularly if they are feeling unwell. The NHS website has a good resource for this.
Health Canada	**Product Monograph** The Health Canada Comirnaty Product Monograph was authorised on 16 September 2021. The Pfizer-BioNTech COVID-19 vaccine was authorized for use in Canada under the Interim Order respecting the importation, sale and advertising of drugs for use in relation to COVID-19. The interim order expired on September 16, 2021. On this date, Pfizer-BioNTech Comirnaty® transitioned to an authorization under the *Food and Drug Regulations.* [TRIM D21-3152230] Section 7.1.1 Pregnant Women is referenced in Section 7 – Warnings and Precautions of the Product Monograph: 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). Section 16 – Non-clinical toxicology addresses reproductive and developmental Toxicology: Reproductive and Developmental Toxicology: In a reproductive and developmental toxicity study, 30 mcg/animal (0.06 mL of a vaccine formulation containing the same quantity of nucleoside-modified messenger ribonucleic acid (mRNA) and other ingredients included in a single human dose) of COMIRNATY 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. Section 7.1.2 Breast-feeding is referenced in Section 7 – Warnings and Precautions of the Product Monograph: It is unknown whether COMIRNATY is excreted in human milk. A risk to the newborns/infants cannot be excluded. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for immunization against COVID-19. The Patient Medication Information advises intended vaccine recipient to talk to their healthcare professional prior to receiving the vaccine if they are pregnant, may be pregnant or plan to become pregnant, or are breastfeeding. **National Advisory Committee on Immunization Recommendations** The Canadian Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI) updated their recommendations on the use of COVID-19 vaccines on 28 September 2021. [TRIM D21-3152344]

	The NACI preferentially recommends that a complete vaccine series with an mRNA COVID19 vaccine should be offered to individuals in the authorized age group who are pregnant or breastfeeding. Informed consent should include discussion about emerging evidence on the safety of mRNA COVID-19 vaccines in these populations. (Strong NACI Recommendation) NACI recommends that a viral vector COVID-19 vaccine may be offered to individuals in the authorized age group who are pregnant or breastfeeding to initiate a series when other authorized COVID-19 vaccines are contraindicated or inaccessible. Informed consent should include discussion about the risk and symptoms of VITT, the need to seek immediate medical care should symptoms develop, as well as the limited evidence on the use of viral vector COVID-19 vaccines in these populations. (Discretionary NACI Recommendation) The *Canadian COVID-19 Vaccines Registry for Pregnant and Lactating Individuals: An Evaluation of Safety, Effectiveness & Acceptability* is hosted by the University of British Columbia (UBC) and the Women's Health Research Institute (WHRI) and funded by the Public Health Agency of Canada. The purpose of this study is to collect data from pregnant, recently pregnant, and lactating women & individuals, regardless of whether they have received a COVID-19 vaccine, to assess the safety and effectiveness of COVID-19 vaccines and to examine attitudes towards COVID-19 vaccination in this population.
	Relevant regulatory action N/A
NZ Medsafe	**Datasheet** The New Zealand Comirnaty Data Sheet version: pfdcovii10921 was last updated on 6 September 2021. [TRIM D21-3152424] Section 4.6 of the Data Sheet addresses Fertility, pregnancy and lactation. Fertility - In a combined fertility and developmental toxicity study, female rats were intramuscularly administered COMIRNATY prior to mating and during gestation (4 full human doses of 30 µg each, spanning between pre-mating day 21 and gestation day 20). SARS-CoV-2 neutralising antibodies were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in fetuses and offspring. There were no vaccine related effects on female fertility and pregnancy rate. 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. Lactation - It is unknown whether BNT162b2 [mRNA] is excreted in human milk. A combined fertility and developmental toxicity study in rats did not show harmful effects on offspring development before weaning (see Fertility). **Relevant regulatory action** N/A
Other international regulators (via ICMRA PV Network and ACCESS)	At the 20 July 2021 International Coalition of Medicines Regulatory Authorities (ICMRA) Pharmacovigilance Network meeting one of the Topics of special Interest was COVID-19 vaccines within pregnancy. s33 s33

	The FDA reported on a plan for pregnancy safety studies for COVID-19 vaccines. s33 [redacted] Health Canada reported that a pregnancy register has been established, but no data was available at the time of the meeting. MHRA reported that epidemiological studies were planned by public health agencies for Scotland and England. They were unlikely to have full data until 2022. Both Health Canada and the MHRA advised the meeting that with the current limited data, no safety concerns have been identified at this time. On 9 February 2021, ICMRA convened the *Pregnancy and Lactation Workshop* in the context of COVID-19 vaccination. [TRIM D21-3151446] It was acknowledged that pregnant and breastfeeding women have not been included in the clinical trials for COVID-19 vaccines but that many of them will or could be vaccinated. One of the objectives of the workshop was to identify opportunities for international collaboration and develop a global strategy aimed at obtaining systematic information on these population groups.

5. Other information

s33 [redacted]

s33

[redacted]

Literature	A PubMed search for miscarriage/ spontaneous abortion identified the article by Herbert, Lucke & Dodson (2009)[2] who present the findings on Pregnancy Losses in Young Australian Women using data from the Australian Longitudinal Study on Women's Health. The loss of pregnancies due to miscarriages ranges from an estimated 1 in 3 to 1 in 5 pregnancies. The rate of stillbirths in developed countries including Australia has been estimated to be 5.3 per 1,000 deliveries for women aged 15 to 44 years. The search also identified the article by Black et al (2009)[3] that discusses the importance of understanding background rates of disease in the assessment of vaccine safety during the mass vaccination with pandemic H1N1 influenza vaccines. They report that based on a UK rate of 12% of pregnancies ending in spontaneous abortion/ miscarriage, if 1 million pregnant women were vaccinated

[2] Herbert,D, Lucke, j, Dodson, A, PREGNANCY LOSSES IN YOUNG AUSTRALIAN WOMENFindings from the Australian Longitudinal Study on Women's Health, *Women's Health Issues* 19 (2009) 21–29 [TRIM D20-3800964]

[3] Black, S, Eskola, J, Siegrist, CA, Halsey, N, MacDonald, N, Law, B, Miller, E, Andrews, N, Stowe, J, Salmon,D, Vannice, K, Izurieta, HS, Akhtar, A, Gold, M, Oselka, G, Zuber, P, Pfeifer, D, Vellozzi, C, Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vaccines, *The Lancet* 2009 vol 374, pp2115-22 DOI:10.1016/S0140-6736(09)61877-8 [TRIM D20-3568377]

with the influenza vaccine, you would expect 397 events within 1 day, 2780 events within 7 days, and 16684 events within 6 weeks of vaccination.

A PubMed search for COVID-19 disease in pregnant women identified the article by Villar, Ariff, & Gunier (2021)[4] who present findings from the Maternal and Neonatal Morbidity and Mortality among Pregnant Women with and without COVID-19 Infection The INTERCOVID Multinational Cohort Study. The findings of the study indicates a consistent association between pregnant individuals with COVID-19 diagnosis and higher rates of adverse outcomes, including maternal mortality, preeclampsia, and preterm birth compared with pregnant individuals without COVID-19 diagnosis.

A Pub Med search for COVID-19 vaccination in pregnant women identified the article by Shimabukuro et al (2021)[5] who report preliminary findings of mRNA COVID-19 vaccine safety monitoring systems: the "v-safe after vaccination health checker" surveillance system, the v-safe pregnancy registry, and the Vaccine Adverse Event Reporting System (VAERS).

From December 14, 2020, to February 28, 2021, data from the "v-safe after vaccination health checker" surveillance system, the v-safe pregnancy registry, and the Vaccine Adverse Event Reporting System (VAERS) was used to characterize the initial safety of mRNA Covid-19 vaccines in pregnant persons.

A total of 35,691 v-safe participants 16 to 54 years of age identified as pregnant. Injection-site pain was reported more frequently among pregnant persons than among nonpregnant women, whereas headache, myalgia, chills, and fever were reported less frequently. Among 3958 participants enrolled in the v-safe pregnancy registry, 827 had a completed pregnancy, of which 115 (13.9%) were pregnancy losses and 712 (86.1%) were live births (mostly among participants vaccinated in the third trimester). Adverse neonatal outcomes included preterm birth (in 9.4%) and small size for gestational age (in 3.2%); no neonatal deaths were reported. Although not directly comparable, calculated proportions of adverse pregnancy and neonatal outcomes in persons vaccinated against Covid-19 who had a completed pregnancy were similar to incidences reported in studies involving pregnant women that were conducted before the Covid-19 pandemic. Among 221 pregnancy-related adverse events reported to the VAERS, the most frequently reported event was spontaneous abortion (46 cases).

Preliminary findings did not show obvious safety signals among pregnant persons who received mRNA Covid-19 vaccines. However, more longitudinal follow-up, including follow-up of large numbers of women vaccinated earlier in pregnancy, is necessary to inform maternal, pregnancy, and infant outcomes.

The search also identified the article by Beharier and Mayo et al[6] who explored maternal and neonatal responses to the Pfizer BNT162b2 SARS-CoV-2 mRNA vaccine. The authors examined blood samples from women and cord blood of neonates following childbirth. Samples were stratified into three groups: vaccine recipients, unvaccinated participants with past positive SARS-CoV-2 test, and

[4] Villar,J, Ariff,S, Gunier,RB, Maternal and Neonatal Morbidity and Mortality Among Pregnant Women With and Without COVID-19 Infection The INTERCOVID Multinational Cohort Study, *JAMA Pediatr.* 2021;175(8):817-826. doi:10.1001/jamapediatrics.2021.1050 [TRIM D21-3162266]

[5] Shimabukuro, T, Shin, K, Myers,TR, Moro, PR, Panagiotakopoulos, TOL, Marquez, PL, Olson, CK, Chang, RLKT, Ellington, SR, Burkel, VK, et al., for the CDC v-safe COVID-19 Pregnancy Registry Team, 2021 Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons, *The New England Journal of Medicine*, vol.384, p. 2273-2282 DOI: 10.1056/NEJMoa2104983 [TRIM D21-3150281]

[6] Beharier,O, Neeman, M, Kovo, M, Efficient maternal to neonatal transfer of antibodies against SARS-CoV-2 and BNT162b2 mRNA COVID-19 vaccine, *J Clin Invest*. 2021;131(13):e150319. https://doi.org/10.1172/JCI150319 [TRIMD21-3169604]

	unvaccinated participants without prior infection. Vaccinated mothers and mothers with previous infection generated and transferred protective IgG antibodies across the placenta. This study provides evidence to support the efficacy of COVID-19 vaccination in pregnancy with protection to the neonate against infection, outlining clear vaccine benefits for both maternal and child health.
Biological plausibility	As the product information outlines, there is limited experience with use of COMIRNATY in pregnant women, but animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition or post-natal development. This review has not identified a mechanism by which the PF vaccine could result in adverse pregnancy outcomes
Impact on the Aboriginal and Torres Strait Islander peoples	No relevant case reports submitted to the TGA's AEMS identified as Aboriginal and Torres Strait Islander peoples in the ethnicity field. There are no specific recommendations for Aboriginal and Torres Strait Islander peoples at this time noting that underreporting of Indigenous status data in the TGA's AEMS may impact on the ability to identify specific issues for these peoples.

6. Conclusion

Conclusion	The preliminary findings available at this time, from studies in pregnant women who have received mRNA COVID-19 vaccines indicate that the benefits for pregnant women and their babies in being vaccinated and therefore protected from COVID-19 disease outweigh the risks to their health from the vaccine and COVID-19 disease if unvaccinated.. It is the conclusion of this review that based on the current information there is insufficient evidence to suggest that vaccination with Comirnaty is harmful for pregnant women or their babies. However, more information about the safety of mRNA vaccines for pregnant women and their babies will become available as more longitudinal follow-up is completed, including follow-up of large numbers of women vaccinated earlier in pregnancy. The initial signal of a possible higher rate of spontaneous abortion among PF vaccine recipients compared to AZ vaccine recipients was not verified in this review.	
Proposed action	☐**Refer to Stream B – MAVIS Evaluation Stream** ☐**Refer to Stream C – Regulatory Outcomes Stream (ROS)** ☒**Routine monitoring**	
Instructions for Stream B, MAVIS Evaluation Stream (if applicable)	N/A	
Instructions for Stream C, ROS (if applicable)	**Proposed regulatory action**	
	☐PI/CMI update	☐Recall
	☐Safety alert	☐IPMST topic
	☐Medicines Safety Update (MSU)	☐Pregnancy Category update
	☐DHCP Letter	☐External/Internal liaison (specify)
	☐RMP update	☐Other (specify)

	Statement on validity/public health impact
	N/A
	Specific instructions for selected regulatory action(s)
	N/A

References

Pregnancy – Background rates

Herbert,D, Lucke, j, Dodson, A, PREGNANCY LOSSES IN YOUNG AUSTRALIAN WOMEN Findings from the Australian Longitudinal Study on Women's Health, *Women's Health Issues* 19 (2009) 21–29 [TRIM D20-3800964]

Black, S, Eskola, J, Siegrist, CA, Halsey, N, MacDonald, N, Law, B, Miller, E, Andrews, N, Stowe, J, Salmon,D, Vannice, K, Izurieta, HS, Akhtar, A, Gold, M, Oselka, G, Zuber, P, Pfeifer, D, Vellozzi, C Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vaccines, *The Lancet* 2009 vol 374, pp2115-22 DOI:10.1016/S0140-6736(09)61877-8 [TRIM D20-3568377]

COVID-19 Disease and pregnancy

Villar,J, Ariff,S, Gunier,RB, Maternal and Neonatal Morbidity and Mortality Among Pregnant Women With and Without COVID-19 Infection The INTERCOVID Multinational Cohort Study, *JAMA Pediatr.* 2021;175(8):817-826. doi:10.1001/jamapediatrics.2021.1050 [TRIM D21-3162266]

COVID-19 vaccination and pregnancy

Beharier,O, Neeman, M, Kovo, M, Efficient maternal to neonatal transfer of antibodies against SARS-CoV-2 and BNT162b2 mRNA COVID-19 vaccine, *J Clin Invest*. 2021;131(13):e150319. https://doi.org/10.1172/JCI150319 [TRIMD21-3169604]

Burd,I, Kino, T, Segars,J, The Israeli study of Pfizer BNT162b2 vaccine in pregnancy: considering maternal and neonatal benefits *J Clin Invest.* 2021;131(13):e150790. https://doi.org/10.1172/JCI150790 [TRIM D21-3169335]

Shimabukuro, T, Shin, K, Myers,TR, Moro, PR, Panagiotakopoulos, TOL, Marquez, PL, Olson, CK, Chang, RLKT, Ellington, SR, Burkel, VK, et al., for the CDC v-safe COVID-19 Pregnancy Registry Team, 2021 Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons, *The New England Journal of Medicine*, vol.384, p. 2273-2282 DOI: 10.1056/NEJMoa2104983 [TRIM D21-3150281]

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Document 5

Australian Government
Department of Health

Surveillance and Targeted Review Stream (STRS) – Targeted Investigation Process (TIP) for vaccines

Medicines and Vaccines Investigation and Surveillance Section

TRIM reference:
D21-3272299

Comirnaty (BNT162b2 [mRNA]) COVID-19 vaccine and spontaneous abortion

Date and Time completed	29/10/2021 10:00 AM

Summary

This is the second Targeted Investigation Process (TIP) conducted on the vaccine-event pair Comirnaty (BNT162b2 [mRNA]) COVID-19 Vaccine Pfizer (PF) and *spontaneous abortion*. The original TIP was completed on 6 October 2021 with the recommendation to continue monitoring reports of pregnancy and foetal-related adverse events following vaccination with COVID-19 vaccines through routine pharmacovigilance processes. Given the significant public interest in this topic, this second TIP was internally requested following identification of further relevant case reports in the TGA's Adverse Events Management System (AEMS).

Spontaneous abortion, which is the loss of a pregnancy without outside intervention before 20 weeks gestation, affects up to 20 percent of recognised pregnancies. About 30 to 50 percent of all pregnancies end prior to recognition. Spontaneous abortion can be subdivided into threatened abortion, inevitable abortion, incomplete abortion, missed abortion, septic abortion, complete abortion, and recurrent spontaneous abortion. Chromosomal abnormalities are causative in approximately 50 percent of spontaneous abortions; multiple other factors may also play a role including infection, improper implantation of fertilised egg in the uterine lining, certain medications, and chronic conditions such as uncontrolled diabetes or thyroid disease.

The Australian Technical Advisory Group on Immunisation (ATAGI) advises that pregnant people are a priority group for COVID-19 vaccination and should be routinely offered an mRNA COVID-19 vaccine, Comirnaty (PF) or Spikevax (elasomeran) COVID-19 Vaccine at any stage of pregnancy. mRNA vaccines are the preferred COVID-19 vaccines for people who are pregnant. Both Comirnaty and Spikevax are category B1 products in the Australian categorisation system and database for prescribing medicines in pregnancy. Pregnant women who cannot access an mRNA vaccine can consider vaccination with Vaxzevria ChAdOx1-S (AZ), previously known as COVID-19 Vaccine AstraZeneca (ChAdOx 1-S). Vaxzevria is a category B2 product.

A review of reports to the TGA's AEMS database on 28 October 2021 identified a total of 66 reports associated with PF and the MedDRA preferred terms (PTs) relating to abortion which include *spontaneous abortion, missed abortion, incomplete spontaneous abortion* and *threatened abortion*. There were 14 reports associated with AZ, and 2 reports associated with Spikevax and the related PTs.

The reporting rates for spontaneous abortion in the 20-29 year age group are similar between AZ and PF. For the 30-39 and 40-49 year age groups, the AZ rate of spontaneous abortion is almost double the PF rate. The reason for the discrepancy in reporting rates for the 30-39 and 40-49 year age groups is not clear and the numbers of reports are small. There are also two case reports for spontaneous abortion (and related PT's) with Spikevax at this time, one each in the 30-39 and 40-49 year age groups. As pregnancy status is not recorded in the vaccine dosage data, these rates are derived from all females in the 20-49 years age group. The UK Medicines and Healthcare products Regulatory Agency (MHRA) however, has observed that the numbers

of reports of miscarriage and stillbirth are low in relation to the number of pregnant women who have received COVID-19 vaccines to date.

The MedDRA PTs relating to abortion did not flag for PF or AZ in the July to August 2021 Disproportionality Analysis Report (DPAR). This data does not include Spikevax because the product was only available on the Australian market from August 2021.

The Australian and other international product information (PI) for PF provide similar warnings on use during pregnancy, advising that 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/foetal development, parturition, or post-natal development. Administration of Comirnaty in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus.

The Australian, Canadian and United Kingdom National Immunisation Technical Advisory Groups (NITAGs) all preference the use of mRNA vaccines for people who are pregnant. The United States national advisory body, the Advisory Committee on Immunisation Practices (ACIP) advises that any of the currently FDA-approved or FDA-authorised COVID-19 vaccines can be administered to people in these groups and does not state a product preference. These NITAGs all agree that all pregnant women should receive COVID-19 vaccination at any stage of pregnancy. This is based on research that has shown that the risk of severe outcomes from COVID-19 is significantly higher for pregnant women and their unborn baby.

The Sponsor's (PF) Periodic Safety Update Report provides an update on *Special Patient Populations* which includes *Use in Pregnant/Lactating Women*. The update, which includes information about the outcome of cases of pregnancy in clinical studies, post authorisation data and a literature review, concluded that no safety signals emerged from a review of these cases of use in pregnant/lactating women.

The MHRA's analysis of the safety of COVID-19 vaccines in pregnancy concludes that there is no pattern from the reports to suggest that any of the COVID-19 vaccines used in the UK (PF, AZ and Spikevax), or any reactions to these vaccines, increase the risk of miscarriage or stillbirth.

The United States Centers for Disease Control (CDC), the Public Health Agency of Canada, and the European Medicines Agency (EMA) have all established registries or safety monitoring studies for COVID-19 vaccines in pregnancy.

A literature search conducted on 28 October 2021 identified two recent publications on COVID-19 vaccination in pregnancy. The first, a case-control study by Magnus *et al* (2021)[1] concluded that there was no evidence of an increased risk for early pregnancy loss after COVID-19 vaccination. The second, a literature review by Joubert *et al* (2021)[2] reported that post-marketing surveillance results have so far shown no safety concerns and no serious vaccine related adverse events related to COVID-19 vaccination in pregnant women with novel mRNA vaccines. These findings are in line with the results from the literature review conducted in the original TIP.

It is the conclusion of this review that based on the current information there is still insufficient evidence to suggest that vaccination with PF is harmful for pregnant women or their babies. The initial statistical signal of a possible higher rate of spontaneous abortion among PF vaccine recipients compared to AZ vaccine recipients was not verified as a validated safety signal in this review.

Recommendations

It is the recommendation of this review to continue to monitor reports of pregnancy and foetal-related adverse events following vaccination with COVID-19 vaccines through routine pharmacovigilance processes including environmental scanning of published literature and monitoring the findings from the COVID-19 vaccine pregnancy registers that have been established in the United States, Canada and Europe.

Priority

High

DISCLAIMER: The purpose of this report is to provide a targeted assessment (at a point in time) of the described vaccine-event pair to assist with triage of workflow. It does not constitute a full evaluation nor a regulatory decision.

1. List of abbreviations

Abbreviation	Meaning
ACCESS	Australia-Canada-Singapore-Switzerland-United Kingdom (consortium)
ADR/AE	Adverse Drug Reaction / Adverse Event
AEFI	Adverse Event Following Immunisation
AEMS	Adverse Event Management System
AESI	Adverse Event of Special Interest
AIR	Australian Immunisation Register
ARTG	Australian Register of Therapeutic Goods
ATAGI	Australian Technical Advisory Group on Immunisation
ATC	Anatomical Therapeutic Chemical (classification system)
AZ	Vaxzevria ChAdOx1-S, previously COVID-19 Vaccine AstraZeneca
CMI	Consumer Medicine Information
COVID-19	Coronavirus disease 2019
DHCPL	Dear Healthcare Professional Letter
DPAR	Disproportionality Analysis Report
EMA	European Medicines Agency (European Union)
FDA	Food and Drug Administration (United States)
GACVS	Global Advisory Committee on Vaccine Safety
IC	Information Component
ICMRA	International Coalition of Medicines Regulatory Authorities
IPMST	International Post Market Surveillance Teleconference
MaVIS	Medicines and Vaccines Investigation and Surveillance
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency (United Kingdom)
MSSR	Monthly Safety Summary Report

MSU	Medicines Safety Update
NCIRS	National Centre for Immunisation Research and Surveillance
O/E	Observed vs. Expected (analysis)
PF	Comirnaty (BNT162b2 [mRNA]) COVID-19 Vaccine Pfizer
PI	Product Information
PRAC	Pharmacovigilance Risk Assessment Committee
PRR	Proportional Reporting Ratio
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
RMP	Risk Management Plan
ROS	Regulatory Outcomes Stream
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SPC/SmPC	Summary of Product Characteristics
STRS	Surveillance and Targeted Review Stream
TIP	Targeted Investigation Process
VERA	Vaccine Epidemiology and Rapid Action
VSIG	Vaccine Safety Investigation Group
WHO-UMC	World Health Organisation – Uppsala Monitoring Centre

2. Vaccine information

Indication(s)	COMIRNATY (BTN162b2 [mRNA]) COVID-19 Vaccine Pfizer (PF): Provisional approval for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older. [TRIM: D21-3158471].
Vaccine roll-out status	All people aged 12 years to 59 years are able to book an appointment for PF. You should not receive this vaccine if you have had: • anaphylaxis (a type of severe allergic reaction) to a previous dose of an mRNA COVID-19 vaccine (i.e., Comirnaty or Spikevax) • anaphylaxis after exposure to any component of the vaccine, including polyethylene glycol (PEG) • myocarditis and/or pericarditis attributed to a previous dose of an mRNA COVID-19 vaccine (i.e., Comirnaty or Spikevax) • any other serious adverse event, that following review by an experienced immunisation provider or medical specialist was attributed to a previous dose of an mRNA COVID-19 vaccine (i.e., Comirnaty or Spikevax) and without another cause identified. PF is preferred over Vaxzevria ChAdOx1-S (AZ) in people aged < 60 years. This is based on the higher risk and observed severity of thrombosis and thrombocytopenia syndrome (TTS) in people < 60 years compared to those ≥ 60.

	However, AZ can be used in adults aged < 60 years if PF if the person has made an informed decision based on an understanding of the risks and benefits. In outbreak settings, adults <60 years of age should strongly consider AZ if they are unable to access PF. Pregnant people are a priority group for COVID-19 vaccination and should be routinely offered an mRNA COVID-19 vaccine (PF or Spikevax) at any stage of pregnancy. mRNA vaccines are the preferred COVID-19 vaccines for people who are pregnant. This is based on the growing body of evidence supporting the safety of mRNA vaccines in pregnancy, while there are still very limited data on the safety of viral vector vaccines (such as Vaxzevria) in pregnancy. This is the advice of the Australian Technical Advisory Group on Immunisation (ATAGI) *Clinical guidance on use of COVID-19 vaccine in Australia in 2021 (v7.3),* last updated on 8 October 2021, [TRIM: D21-3254667] The Department of Health has published guidance: *COVID-19 vaccination decision guide for women who are pregnant, breastfeeding or planning pregnancy version 6 - updated on 15 September 2021* [TRIM: D21-3140558]. This guide has not been updated since the original TIP [TRIM: D21-3183500].
Mechanism of action	The nucleoside-modified messenger RNA in Comirnaty is formulated in lipid nanoparticles, which enable delivery of the non-replicating RNA into host cells to direct transient expression of the SARS-CoV-2 spike (S) antigen. The mRNA codes for membrane-anchored, full-length S with two-point mutations within the central helix. Mutation of these two amino acids to proline locks S in an antigenically preferred prefusion conformation. Comirnaty elicits both neutralising antibody and cellular immune responses to the antigen, which may contribute to protection against COVID-19.

3. Adverse event information

Signal Source	This is the second TIP conducted on the vaccine-event pair PF and *spontaneous abortion*. The original TIP was completed on 6 October 2021 with the recommendation to continue monitoring reports of pregnancy and foetal-related adverse events following vaccination with COVID-19 vaccines through routine pharmacovigilance processes [TRIM: D21-3183500]. Given the significant public interest in this topic, this second TIP was internally requested following identification of further relevant case reports in the TGA's Adverse Events Management System (AEMS) [TRIM: D21-3268661].
AESI status	Pregnancy and birth outcomes are listed as a Category 4 outcome. They were added to the AESI list by the TGA following clinical evaluation and the potential for COVID-19 vaccines to be administered to pregnant women as off-label usage. Please refer to the original TIP [TRIM: D21-3183500] for more details.
AEFI	Spontaneous abortion is the loss of a pregnancy without outside intervention before 20 weeks' gestation. Please refer to the original TIP [TRIM: D21-3183500] for more details.
Magnitude of signal	TGA DPAR The MedDRA preferred terms (PTs) relating to abortion, which include *spontaneous abortion, missed abortion, incomplete spontaneous abortion* and

threatened abortion did not flag for PF or AZ in the July to August 2021 DPAR. [TRIM: D21-3110301]

This data does not include Spikevax because the product was only available on the Australian market from August 2021.

Reporting rates

A comparison of the TGA reporting rates by age groups between PF, AZ and Spikevax for spontaneous abortion and related PT's* to describe miscarriage up to and including 26 October 2021

Age	20-29 yrs	30-39 yrs	40-49 yrs
PF			
Doses for females	2155291	2574596	2509507
Reports	11	47	6
Reporting Rate per 100,000 doses	**0.51**	**1.83**	**0.24**
AZ			
Doses for females	342889	332006	232130
Reports	2	11	1
Reporting Rate per 100,000 doses	**0.58**	**3.31**	**0.43**
SpikeVax			
Doses for females	42728	45332	34919
Reports	0	1	1
Reporting Rate per 100,000 doses	**0**	**2.21**	**2.86**

*missed abortion, incomplete spontaneous abortion, threatened abortion.

Note – Two PF case reports did not provide the age of the patient and are not included on the table.

The reporting rates for spontaneous abortion in the 20-29 year age group are similar between AZ and PF. For the 30-39 and 40-49 year age groups, the AZ rate is almost double the PF rate. The reason for the discrepancy in reporting rates for the 30-39 and 40-49 year age groups is not clear and the numbers of reports are small.

There have been two case reports for spontaneous abortion (and related PT's) with Spikevax at this time, one each in the 30-39 and 40-49 year age groups. Spikevax is relatively new to the COVID-19 vaccination roll out, and as less than 100,000 doses have been administered to females in each age group, the reporting rate described above may not be an accurate representation of the true reporting rate.

The accuracy of the calculated reporting rate is impacted by several considerations including:

- The Australian Immunisation register, used to calculate dosage numbers, does not identify people who are pregnant, so the exposure to the vaccine is based on all females between the ages of 20-49 years.
- In at least nine of the 66 case reports related to PF and abortion, the reporter identified that they were unaware of their pregnancy at the time of vaccination.

	• Early onset spontaneous abortion is often under-identified and consequently under-reported. The dose numbers for females for PF, AZ and Spikevax up to an including 26/10/2021 were obtained via QLIK on 28/10/2021. [TRIM: D21-3269459]. The number of case reports were identified in a QLIK search undertaken on 28/10/2021. The PCDs for PF are filed in TRIM: D21-3269545. The PCDs for AZ are filed in TRIM: D21-3269550. The PCDs for Spikevax are filed in TRIM: D21-3269552. Observed vs. Expected (O/E) analysis Advice received from Vaccine Epidemiology and Rapid Action (VERA) is that an O/E analysis is not possible on this signal due to a lack of available denominator data (i.e. the number of pregnant women who have been vaccinated with PF or any of the other vaccines) in the Australian Immunisation Register.
No. of AEFI reports	**PF Vaccine** A QLIK search was undertaken on 28/10/2021 using the default bookmark, the tradename *Comirnaty* and the *Pregnancy, puerperium and perinatal conditions* SOC. The search identified 87 case reports. The Preferred terms (PTs) reported included*: • 63 reports of spontaneous abortion, • 4 reports each of foetal death and foetal hypokinesia, • 3 reports of stillbirth, • 2 reports each of ectopic pregnancy, gestational hypertension, haemorrhage in pregnancy and premature delivery, and; • a single report each of the following: missed abortion, incomplete spontaneous abortion, threatened abortion, foetal growth abnormality, foetal growth restriction, foetal placental thrombosis, morning sickness, polyhydramnios, premature labour, premature rupture of membranes, premature separation of placenta, threatened labour, abnormal uterine contractions, and uterine contractions during pregnancy. The PCDs for the 87 reports are filed in TRIM: D21-3269636. *Note that more than one PT can be included in each case report. In terms of age group, 91% (79 cases) are in the 18-44 age group, 4.5% (4 cases) are in the 45-64 age group and for 4.5% (4 cases) the age was not provided in the report. In terms of doses, of the 87 case reports, 31.0% (27 cases) were reported following dose one, 42.5% (37 cases) were reported following dose two and 26.5% (23 cases) did not report the dose information. The management of the events reports were as follows: • 16 cases reported management by a GP • 14 cases reported management in a hospital ED • 11 cases reported a hospital admission • 2 case reports reported self • 5 case reports reported unknown • 39 case reports did not complete this field.

The outcome of the reaction reported:

- 18 cases were reported as not recovered / not resolved / ongoing
- 22 cases were reported as recovered / resolved
- 4 cases were reported as recovered / resolved with sequelae
- 8 cases were reported as recovering / resolving
- 35 cases the outcome was reported as unknown.

There were no fatal outcomes reported.

AZ Vaccine

A QLIK search was undertaken on 28/10/2021 using the default bookmark, the tradename *COVID-19 Vaccine AstraZeneca* and the *Pregnancy, puerperium and perinatal conditions* SOC.

This search identified 14 case reports. The Preferred terms (PTs) reported were*: 14 reports of spontaneous abortion and 1 report of ectopic pregnancy with contraceptive device.

The PCDs for the 14 reports are filed in TRIM: D21-3269760.
*Note that more than one PT can be included in each case report.

In terms of age group, 100% (14 cases) are in the 18-44 age group.

In terms of doses, of the 14 case reports, 71.4% (10 case reports) were reported following dose one and 28.6% (4 case reports) were reported following dose two.

The management of the events reports:

- 5 cases reported management by a GP
- 5 cases reported management in a hospital ED
- 4 case reports did not complete this field.

The outcome of the reaction reported:

- 2 cases were reported as not recovered / not resolved / ongoing
- 3 cases were reported as recovered / resolved
- 1 case was reported as recovering / resolving
- 8 cases the outcome was reported as unknown.

There were no fatal outcomes reported.

Spikevax vaccine

A QLIK search was undertaken on 28/10/2021 using the default bookmark, the tradename *COVID-19 Vaccine AstraZeneca* and the *Pregnancy, puerperium and perinatal conditions* SOC.

This search identified 2 case reports. The Preferred terms (PTs) reported were: 2 reports of spontaneous abortion.

The PCDs for the 2 reports are filed in TRIM: D21-3269798.

In terms of age group, 100% (2 cases) are in the 18-44 age group.

In terms of doses, of the 2 case reports, 50% (1 case report) were reported following dose one and 50% (1 case report) were reported following dose two.

s22 [redacted]

There were no fatal outcomes reported.

Summary of AEFI reports	A high-level review of the case reports in the TGA's Adverse Events Management System was conducted focusing on PF and the following PTs relating to abortion: • spontaneous abortion • missed abortion • incomplete spontaneous abortion • threatened abortion. This identified 66 case reports. Of the 66 case reports, nine cases reported that they were unaware of their pregnancy at the time of vaccination. 18 cases reported provided no narrative or times to onset of the AEFI reported. Many of the case reports related to pregnancy prior to 12 weeks. Several reporters stated that they did not think that the AEFI was related to the vaccine but submitted a report as it was new vaccine. The AEFI reports demonstrate the temporal relation of spontaneous abortion and the administration of PF. However, given the high rate for spontaneous abortion which ranges from an estimated 1 in 3 to 1 in 5 of all pregnancies it is difficult to assess causality.[3]

4. Regulatory surveillance

Local, including: **PI, Sponsor's PSUR/MSSR, and applicable clinical guidance**	**Product Information (PI)**
	The Australian Product Information for Comirnaty version: pfpcovii20921 was revised on 21 September 2021. [TRIM: D21-3158471]. **Section 4.6 Fertility, pregnancy and lactation** **Effects on fertility** In a combined fertility and developmental toxicity study, female rats were intramuscularly administered COMIRNATY prior to mating and during gestation (4 full human doses of 30 µg each, spanning between pre-mating day 21 and gestation day 20). SARS CoV-2 neutralising antibodies were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in fetuses and offspring. There were no vaccine related effects on female fertility and pregnancy rate. **Use in pregnancy - Pregnancy Category B1*** 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 Effects on fertility). Administration of COMIRNATY in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and fetus. * The Australian categorisation system and database for prescribing medicines in pregnancy have been developed by medical and scientific experts based on available evidence of risks associated with taking particular medicines while

pregnant.[i] **Category B1:** Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

Use in lactation
It is unknown whether BNT162b2 [mRNA] is excreted in human milk. A combined fertility and developmental toxicity study in rats did not show harmful effects on offspring development before weaning (see Effects on fertility).

Applicable clinical guidance

The Australian Technical Advisory Group on Immunisation (ATAGI) Clinical guidance on use of COVID-19 vaccine in Australia in 2021 (v7.3) was last updated on 8 October 2021. [TRIM: D21-3254667]

It contains the following guidance for women and adolescents ≥ 12 years who are pregnant, breastfeeding or planning pregnancy:

Pregnant people are a priority group for COVID-19 vaccination and should be routinely offered an mRNA COVID-19 vaccine (Comirnaty or Spikevax) at any stage of pregnancy.

mRNA vaccines (Comirnaty or Spikevax) are the preferred COVID-19 vaccines for people who are pregnant. This is based on the growing body of evidence supporting the safety of mRNA vaccines in pregnancy, while there are still very limited data on the safety of viral vector vaccines (such as Vaxzevria) in pregnancy. However pregnant women who cannot access an mRNA vaccine can consider vaccination with Vaxzevria if the benefits to the individual outweigh the potential risks. Pregnant women who received a first dose of Vaxzevria can receive either an mRNA COVID-19 vaccine (Comirnaty or Spikevax) or Vaxzevria for their second dose, although an mRNA vaccine is preferred.

Women who are breastfeeding or planning pregnancy are preferred to have an mRNA COVID-19 vaccine because of their age (i.e. mRNA vaccines are the preferred vaccines for all people under 60) and because post-marketing studies demonstrate safety of these vaccines in pregnancy. However, there are no theoretical safety concerns associated with the use of Vaxzevria specific to breastfeeding or planning pregnancy, and women in these groups who cannot access an mRNA COVID-19 vaccine should consider vaccination with Vaxzevria, particularly in outbreak settings.

Please refer to the original TIP [TRIM: D21-3183500] for more details.

Sponsor's PSUR/MSSR

The Sponsor's Monthly Summary Safety Report (MSSR) for PF covering the period 01 September through 30 September 2021 was submitted to the TGA on 10 October 2021. [TRIM: D21-3234082]

The internal review of cases indicative of drug exposure during pregnancy for the reporting period included in the MSSR, did not reveal any new safety information. Whether the frequency of pregnancy outcomes, pregnancy related events, and

[i] Prescribing medicines in pregnancy database accessed 28 October 2021. https://www.tga.gov.au/prescribing-medicines-pregnancy-database

	newborn events is consistent with expectation cannot be evaluated based on the spontaneous reports. The number of pregnant women who have received the COVID-19 vaccine is unknown. The MAH is conducting study C4591015 to study the safety of Comirnaty in pregnant women – this study is being conducted as a committed Post-Authorization Safety Study. Other Post-Authorization Safety Studies planned or being conducted may inform regarding pregnancy. The Sponsor's first Periodic Safety Update (PSUR) for PF covering the period 19 December 2020 through 18 June 2021 was submitted to the TGA on 19 August 2021. [TRIM: D21-3029287] The PSUR provides an update on *Special Patient Populations* which includes *Use in Pregnant/Lactating Women*. The update, which includes information about the outcome of cases of pregnancy in the clinical studies, post authorisation data and a literature review concluded that no safety signals emerged from a review of these cases of use in pregnant/lactating women.
US FDA	**Label** The Pfizer-BioNtech COVID-19 Vaccine Fact Sheet and label for Health Care Providers was last updated on 20 October 2021. [TRIM: D21-3254882] Sections 11.1 *Pregnancy*, 11.2 *Lactation*, and the *Comirnaty (Covid-19 Vaccine, mRNA) and Pfizer-BioNtech Covid-19 Vaccine Factsheet for recipients and caregivers* were not amended and are as described in the original TIP [TRIM: D21-3183500]. In summary, the label describes: - insufficient evidence to inform vaccine-associated risks in pregnancy, - no vaccine-related adverse effects on female fertility, fetal development, or postnatal development in an animal reproductive and developmental toxicity study, and; - insufficient data on the effects of Pfizer-BioNTech COVID-19 Vaccine on lactation. **Advisory Committee on Immunisation Practices (ACIP) CDC** The Advisory Committee on Immunisation Practices (ACIP) Centres for Disease Control and Prevention (CDC) *Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Approved or Authorized in the United States* was last updated on 25 October 2021. [TRIM: D21-3256908]. The considerations involving pregnancy, lactation and fertility were not amended in the latest update and are as described in the original TIP. Please refer to TRIM: D21-3183500 for details. The CDC established the v-safe COVID-19 Vaccine Pregnancy Registry to learn more about the safety of COVID-19 vaccines for people who are pregnant. The registry is collecting health information from people who received COVID-19 vaccination in the periconception period (within 30 days before last menstrual period) or during pregnancy. The information is critical to helping people and their healthcare providers make informed decisions about COVID-19 vaccination. Participation is voluntary, and participants may opt out at any time. [TRIM: D21-3150320]

EU EMA	**Summary of Product Characteristics (SmPC)**
	The European Medicines Agency (EMA) Comirnaty Summary of Product Characteristics (SmPC) was last updated on 14 October 2021. [TRIM: D21-3257298] Section 4.6 *Fertility, pregnancy and lactation* and the *Reproductive toxicity* subsection in section 5.3 were not amended in the last update and are as described in the original TIP [TRIM: D21-3183500]. In summary, the SmPC describes: - limited experience with use of Comirnaty in pregnant women, - no indication of direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development in animal studies, and; - insufficient information on whether Comirnaty is excreted in human milk. The EMA is coordinating observational studies in EU Member States looking at real-world data from clinical practice to monitor the safety and effectiveness of COVID-19 vaccines, including in pregnant women.
	Pharmacovigilance Risk Assessment Committee (PRAC)
	N/A
UK MHRA	**Summary of Product Characteristics (SPC)**
	The Comirnaty Summary of Product Characteristics (SPC) was last updated in Oct 2021. [TRIM D21-3258211] Section 4.6 *Fertility, pregnancy and lactation* and the *Reproductive toxicity* subsection in section 5.3 were not amended in the last update and are as described in the original TIP [TRIM: D21-3183500]. In summary, the SmPC describes: - limited experience with use of Comirnaty in pregnant women, - no indication of direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development in animal studies, and; - insufficient information on whether Comirnaty is excreted in human milk.
	Yellow Card reporting / Relevant regulatory action
	The current *Coronavirus vaccine – weekly summary of Yellow Card reporting* covers the period 9 December 2020 to 20 October 2021 and was updated on 28 October 2021. [TRIM: D21-3271199]. Aside from updated statistics, the information in the summary has not changed since the original TIP was completed. The summary includes the following section about the safety of COVID-19 vaccines in pregnancy: Safety of COVID-19 vaccines in pregnancy - The MHRA closely monitors the safety of COVID-19 vaccine exposures in pregnancy, including Yellow Card reports for COVID-19 vaccines used in pregnancy. These reports have been reviewed by the independent experts of the Commission on Human Medicines' COVID-19 Vaccines

	Benefit Risk Expert Working Group and by the Medicines for Women's Health Expert Advisory Group (MWHEAG). Pregnant women have the same risk of getting COVID-19 as non-pregnant women but they may be at an increased risk of becoming severely ill, particularly if they get infected in the third trimester or if they also have underlying medical problems, compared to non-pregnant women. **The current advice of the Joint Committee on Vaccination and Immunisation (JCVI) is that the COVID-19 vaccines should be offered to those who are pregnant at the same time as non-pregnant individuals based on their age and clinical risk group. The Pfizer/BioNTech and Moderna vaccines are currently the preferred vaccines for use during pregnancy**. The numbers of reports of miscarriage and stillbirth are low in relation to the number of pregnant women who have received COVID-19 vaccines to date (more than 95,000 up to end of September 2021 in England and Scotland) and how commonly these events occur in the UK outside of the pandemic. **There is no pattern from the reports to suggest that any of the COVID-19 vaccines used in the UK, or any reactions to these vaccines, increase the risk of miscarriage or stillbirth.** Sadly, miscarriage is estimated to occur in about 20 to 25 in 100 pregnancies in the UK and most occur in the first 12 to 13 weeks of pregnancy (the first trimester). Stillbirths are sadly estimated to occur in about 1 in 200 pregnancies in the UK. A few reports of commonly occurring congenital anomalies and preterm births have also been received. There is no pattern from the reports to suggest that any of the COVID-19 vaccines used in the UK increase the risk of congenital anomalies or birth complications. Pregnant women have reported similar suspected reactions to the vaccines as people who are not pregnant. Like most vaccines and medicines, clinical trials of COVID-19 vaccines in pregnant women were not carried out prior to use of the vaccines in the general population. However, evidence from non-clinical studies of the COVID-19 vaccines available in the UK have not raised any concerns about safety in pregnancy. The COVID-19 vaccines do not contain organisms that can multiply in the body, so they cannot infect an unborn baby in the womb. Extensive international experience for the Pfizer/BioNTech Vaccine and COVID-19 Vaccine Moderna used in pregnancy have also not raised any safety concerns. The MHRA will continue to closely monitor safety data for use of the COVID-19 vaccines in pregnancy, including through evaluation of electronic healthcare record data.
Health Canada	**Product Monograph** The Health Canada Comirnaty Product Monograph was authorised on 16 September 2021. The Pfizer-BioNTech COVID-19 vaccine was authorized for use in Canada under the Interim Order respecting the importation, sale and advertising of drugs for use in relation to COVID-19. The interim order expired on September 16, 2021. On this date, Pfizer-BioNTech Comirnaty® transitioned to an authorization under the *Food and Drug Regulations.* [TRIM: D21-3152230] The *Warnings and Precautions* section of the Product Monograph addresses safety and efficacy in pregnant women and breast-feeding. The *Non-Clinical Toxicology section* addresses reproductive and developmental toxicology. Both sections are as described in the original TIP [TRIM: D21-3183500].

	In summary, the Product Monograph describes: - that the safety and efficacy of Comirnaty in pregnant women have not yet been established, - no indication of direct or indirect harmful effects with respect to pregnancy, embryo/ fetal development, parturition, or post-natal development in animal studies, and; - no information on the excretion of Comirnaty in human milk. The Patient Medication Information advises intended vaccine recipient to talk to their healthcare professional prior to receiving the vaccine if they are pregnant, may be pregnant or plan to become pregnant, or are breastfeeding. The Public Health Agency of Canada is funding *Canadian COVID-19 Vaccines Registry for Pregnant and Lactating Individuals: An Evaluation of Safety, Effectiveness & Acceptability.* The purpose of this study is to collect data from pregnant, recently pregnant, and lactating women & individuals, regardless of whether they have received a COVID-19 vaccine, to assess the safety and effectiveness of COVID-19 vaccines and to examine attitudes towards COVID-19 vaccination in this population. Dates for publication of data from the registry are not available. **Relevant regulatory action** N/A
NZ Medsafe	**Datasheet** The New Zealand Comirnaty Data Sheet version: pfdcovii10921 was last updated on 6 September 2021. [TRIM D21-3152424] Section 4.6 addresses information in relation to *fertility, pregnancy and lactation* and is as described in the original TIP [TRIM: D21-3183500]. In summary, the Data Sheet describes: - limited experience with use of Comirnaty in pregnant women, - no indication direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition or post-natal development in animal studies, and; - no information on the excretion of Comirnaty in human milk. **Relevant regulatory action** N/A
Other international regulators (via ICMRA PV Network and ACCESS)	At the 20 July 2021 International Coalition of Medicines Regulatory Authorities (ICMRA) Pharmacovigilance Network meeting one of the Topics of special Interest was COVID-19 vaccines within pregnancy. The EMA, FDA and Health Canada all reported plans for safety monitoring of COVID-19 vaccines in pregnancy. The MHRA reported that epidemiological studies were planned by public health agencies for Scotland and England. Further information on this network meeting can be found in the original TIP [TRIM: D21-3183500]. Both Health Canada and the MHRA advised the meeting that with the current limited data, no safety concerns have been identified at this time. On 9 February 2021, ICMRA convened the *Pregnancy and Lactation Workshop* in the context of COVID-19 vaccination. [TRIM: D21-3151446]

	It was acknowledged that pregnant and breastfeeding women have not been included in the clinical trials for COVID-19 vaccines but that many of them will or could be vaccinated. One of the objectives of the workshop was to identify opportunities for international collaboration and develop a global strategy aimed at obtaining systematic information on these population groups.

5. Other information

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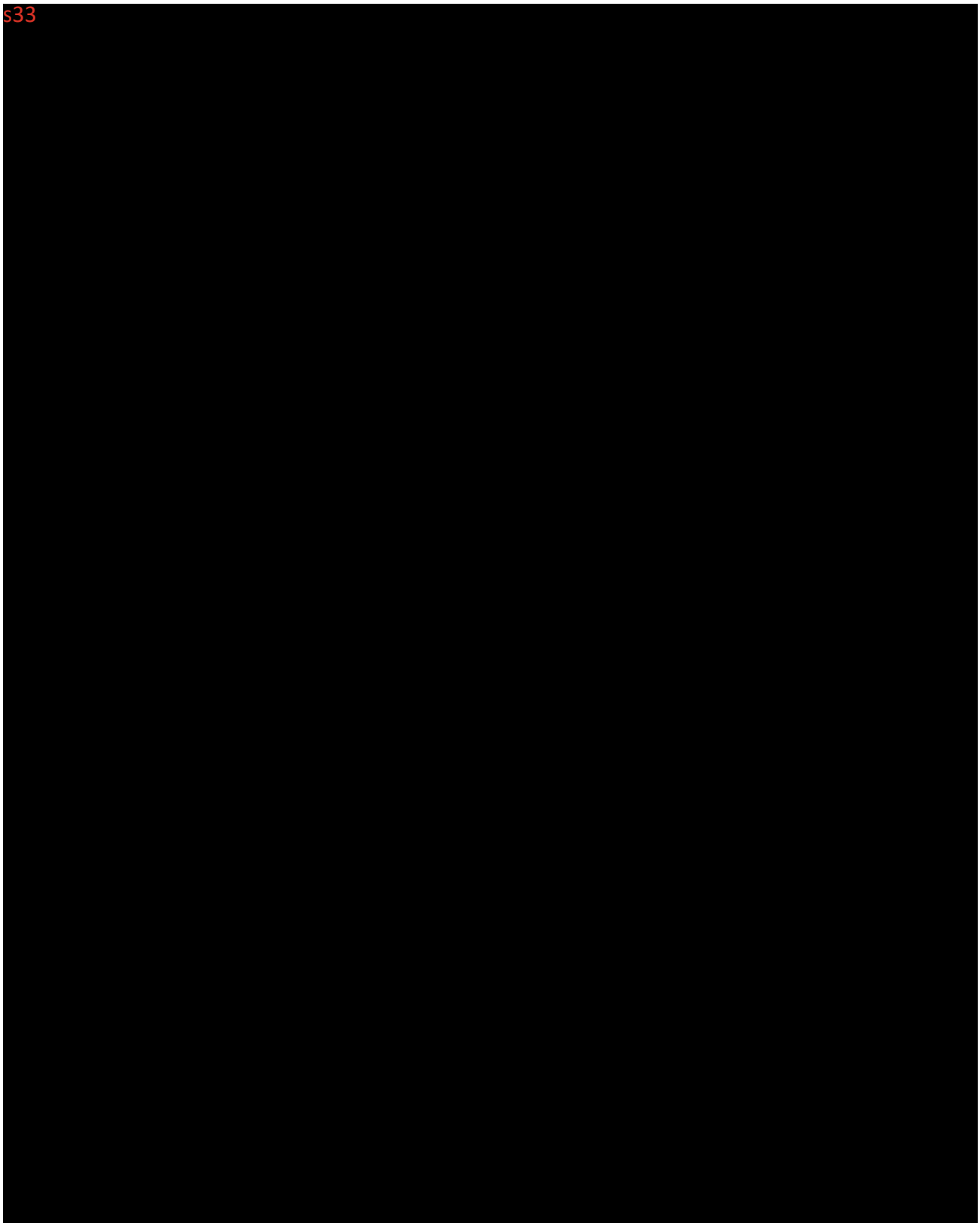

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[redacted]

Literature	A PubMed search conducted on 28 October 2021, using the search terms '*COVID-19*', '*vaccination*' and '*pregnancy*' identified a case-control study by Magnus *et al* (2021)[1] published in the correspondence section of the New England Journal of Medicine. The study used data from 13,956 women with ongoing pregnancies (of whom 5.5% were vaccinated), and 4,521 women with miscarriages (of whom 5.1% were vaccinated), from the Norwegian health registries. The conclusion of the study was that there was no evidence of an increased risk for early pregnancy loss after COVID-19 vaccination. The search also identified an updated literature review by Joubert *et al* (2021)[2], published online ahead of print in the BJOG, on COVID-19 and novel mRNA vaccines in pregnancy. This review concluded that from the over 50,000 pregnant women included on the US v-safe registry, along with a similar registry created by the United Kingdom, results have so far shown no safety concerns and no serious vaccine related adverse events related to COVID-19 vaccination in pregnant women. Please refer to the original TIP [TRIM: D21-3183500] for the further literature search results, as conducted on the original TIP.
Biological plausibility	As the product information outlines, there is limited experience with use of Comirnaty in pregnant women, but animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development,

	parturition or post-natal development. This review has not identified a mechanism by which the PF vaccine could result in adverse pregnancy outcomes.
Impact on the Aboriginal and Torres Strait Islander peoples	No relevant case reports submitted to the TGA's AEMS identified as Aboriginal and Torres Strait Islander peoples in the ethnicity field. There are no specific recommendations for Aboriginal and Torres Strait Islander peoples at this time noting that underreporting of Indigenous status data in the TGA's AEMS may impact on the ability to identify specific issues for these peoples.

6. Conclusion

Conclusion	The preliminary findings available at this time, from studies in pregnant women who have received mRNA COVID-19 vaccines indicate that the benefits for pregnant women and their babies in being vaccinated and therefore protected from COVID-19 disease outweigh the risks to their health from the vaccine and COVID-19 disease if unvaccinated. It is the conclusion of this review that, based on the current information, there is still insufficient evidence to suggest that vaccination with Comirnaty is harmful for pregnant women or their babies. However, more information about the safety of mRNA vaccines for pregnant women and their babies will become available as more longitudinal follow-up is completed, including follow-up of large numbers of women vaccinated earlier in pregnancy. The initial signal of a possible higher rate of spontaneous abortion among PF vaccine recipients compared to AZ vaccine recipients was not verified in this review.	
Proposed action	☐**Refer to Stream B – MAVIS Evaluation Stream** ☐**Refer to Stream C – Regulatory Outcomes Stream (ROS)** ☒**Routine monitoring**	
Instructions for Stream B, MAVIS Evaluation Stream (if applicable)	N/A	
Instructions for Stream C, ROS (if applicable)	**Proposed regulatory action**	
	☐PI/CMI update	☐Recall
	☐Safety alert	☐IPMST topic
	☐Medicines Safety Update (MSU)	☐Pregnancy Category update
	☐DHCP Letter	☐External/Internal liaison (specify)
	☐RMP update	☐Other (specify)
	Statement on validity/public health impact	
	N/A	
	Specific instructions for selected regulatory action(s)	
	N/A	

References

1. Magnus, M., H. Gkessing, H. Eide, *et al.,* Covid-19 Vaccination During Pregnancy and First-Trimester Miscarriage*. N Engl J Med*, 2021. [TRIM D21-3270416]

2. Joubert, E., A. Kekeh, and C. Amin, COVID-19 and Novel mRNA Vaccines in Pregnancy: An Updated Literature Review. *BJOG*, 2021. [TRIM D21-3270420]

3. Herbert, D., Lucke, J., Dodson, A. PREGNANCY LOSSES IN YOUNG AUSTRALIAN WOMEN Findings from the Australian Longitudinal Study on Women's Health, *Women's Health Issues* 19 (2009) 21–29 [TRIM D20-3800964]

Pharmacovigilance Branch, Therapeutic Goods Administration

mRNA COVID-19 vaccines and post-menopausal haemorrhage / bleeding **TRIM: D24-1311692**	
PRODUCT DETAILS	
Innovator tradename	Comirnaty and Spikevax
ADVERSE EVENT DETAILS	
<Describe the adverse event and its severity >	
SIGNAL DETAILS	
Signal notification source	Sponsor notifications [TRIM: D24-1312234] The TGA was notified by the sponsors for Comirnaty and Spikevax that no further actions (including PI updates) would be undertaken in relation to postmenopausal haemorrhage associated with Comirnaty or Spikevax administration. This notification arose following an initial request by the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) that the sponsors of Comirnaty and Spikevax, Pfizer and Moderna respectively conduct updated signal investigations into post-menopausal bleeding with the two vaccines. Both sponsors submitted the signal investigations in which they refute the signal. **On the 8 March 2024** the meeting highlights from the Pharmacovigilance Risk Assessment Committee 4-7 2024 were published on the EMA website. The web statement available at: www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-4-7-march-2024 and filed in TRIM: D24-1311707] *PRAC finds no link between mRNA COVID-19 vaccines and postmenopausal bleeding.* *EMA's safety committee (PRAC) concluded that there was insufficient evidence to establish a causal association between the COVID-19 vaccines Comirnaty and Spikevax and cases of postmenopausal bleeding.* *Postmenopausal bleeding is commonly defined as vaginal bleeding occurring one year or more after the last menstrual period. Postmenopausal bleeding is always considered abnormal and can be a symptom of serious medical conditions.* *Recently, new information emerged from the medical literature as well as post-authorisation data that prompted investigation into postmenopausal bleeding with the two vaccines.*

	The PRAC assessed all available data, including findings from literature, and available post-marketing spontaneous reports of suspected adverse reactions. *After careful review, the PRAC considered that the available data do not support a causal association and an update of the product information for either vaccine is not warranted.* *The committee will continue to monitor this issue for both Comirnaty and Spikevax through the established safety monitoring practices.*
Date received	23/01/2024
Signal context and signal background (if relevant)	To date, the TGA has conducted several signal investigations into menstrual disorders in association with COVID-19 vaccinations. These investigations concentrated mainly on menstrual disorders including heavy bleeding, in women of reproductive age. A recent investigation into menstrual irregularities and COVID-19 vaccines completed in July 2023 recommended that a focused signal investigation be conducted into abnormal uterine bleeding in women outside the reproductive age group (TRIM: D23-5253802). This potential signal is currently listed in the VSS Vaccine SISTA with a medium priority and is awaiting allocation (see D22-5112735).
RECOMMENDATIONS AND PRIORITY	
Impression	The potential signal 'mRNA COVID-19 vaccines and postmenopausal bleeding / haemorrhage' was assessed and refuted by the EMA PRAC in March 2024. The EMA PRAC investigation found that there is no link between mRNA COVID-19 vaccines and postmenopausal bleeding. The TGA has listed a related potential signal of 'abnormal uterine bleeding in women outside the reproductive age group associated with COVID-19 vaccines' for a focused signal investigation with a medium priority. The potential signal can continue to be monitored until such time as the investigation is conducted by VSS.
Record of decision	Completed by Acting VSS Director on 18 April 2024 As noted in this signal assessment, both the EMA and the sponsor's for Comirnaty and Spikevax concluded that there is currently insufficient evidence of an association between mRNA COVID-19 vaccines and postmenopausal bleeding. It is noted that a focused signal investigation into abnormal uterine bleeding in women outside the reproductive age group and COVID-19 vaccines is awaiting allocation through the VSS workflow. This focused signal investigation was recommended following VSS's completion of a signal investigation into menstrual irregularities and COVID-19 vaccines. Although the EMA and sponsors for Comirnaty and Spikevax found insufficient evidence of an association between mRNA COVID-19 vaccines and postmenopausal bleeding, the recommended TGA investigation into a similar signal is still recommended. The purpose

	of this would be to review the Australian data submitted in AEMS, and to collate the findings from the EMA and Comirnaty and Spikevax sponsors regarding this topic. No additional action, or change to the prioritisation of this potential signal in SISTA, is recommended based on this signal assessment notification.

RECOMMENDATION

- [x] Further tasks required - please specify:
- [ ] Refer to Regulatory Outcomes Section
- [ ] Return to routine monitoring