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:
D22-5794110

COMIRNATY and VAXZEVRIA and Type 1 Diabetes Mellitus

Date and Time completed	30/08/2022 11:00 AM

Summary

The source of this Targeted Investigation Process (TIP) was the TGA May – June 2022 disproportionality analysis report (DPAR). Disproportionate reporting of 'type 1 diabetes mellitus' was identified for Comirnaty. The scope of the TIP was expanded to include Vaxzevria when review and reclassification of the cases in the TGA's adverse event monitoring system (AEMS) showed that the reporting rate of this preferred term (PT) was similar for both vaccines.

Although this TIP identified published case reports of the development of diabetic ketoacidosis (DKA) in patients with pre-existing type 1 diabetes following COVID-19 vaccination, the focus was the association between Comirnaty and Vaxzevria and new onset type 1 diabetes.

Type 1 diabetes is an autoimmune condition in which the immune system is activated to destroy the cells in the pancreas which produce insulin. Without insulin, the body's cells cannot turn glucose (sugar), into energy. Treatment is directed toward managing the amount of sugar in the blood using insulin, diet and lifestyle to prevent complications.

Autoimmune diseases, including type 1 diabetes, are thought to develop following environmental exposure in patients with genetic predisposition. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and vaccines against it could represent new environmental triggers for autoimmune endocrine disorders (Patrizio et al, 2021). Importantly however, patients with diabetes are at a high risk of adverse outcomes after COVID-19 infection, and infection itself can be associated with severe hyperglycaemia, including hyperglycaemic emergencies (Ganakumar et al, 2022). The Australian Technical Advisory Group on Immunisation (ATAGI) has identified patients with diabetes as a priority group for vaccination. For example, following provisional approval of a new paediatric formulation of the Spikevax (Moderna) vaccine, ATAGI have recommended COVID-19 vaccination for children aged 6 months to less than 5 years who are at increased risk of severe COVID-19. This includes children with type 1 diabetes [TRIM D22-5839352].

The overall incidence of type 1 diabetes in Australia in 2018 was 12 per 100,000 per year. The incidence is higher in males than females. In general, the incidence is higher in younger age groups, peaking in the pre-school and teenage years.

Diabetes is not listed in any of the TGA or international COVID-19 vaccine product information (PI) documents.

Causality/public health impact

Strength of the association	Overall, the quantitative findings from this TIP do not support a causal association between Comirnaty and type 1 diabetes: • Although there was disproportionate reporting of type 1 diabetes to the TGA in association with Comirnaty only (PRR 3.35), two of the seventeen cases were identified as a duplicate and a Vaxzevria case respectively. With adjusted case numbers, the reporting rates for Vaxzevria (0.36 per million doses) and Comirnaty (0.34 per million doses) were found to be similar. • An age adjusted observed versus expected (OvE) analysis was performed for this TIP. The number of observed cases of type 1 diabetes for both Comirnaty and Vaxzevria was significantly less than the age adjusted expected number of cases. Within the individual age strata, the observed was also significantly less than expected for both vaccines. The Comirnaty Sponsor's age adjusted OvE analyses also found that the reported cases were less than expected. • s33 [redacted] • No formal epidemiological studies of the risk of type 1 diabetes associated with COVID-19 vaccines were located. The published literature consisted mostly of case reports of type 1 diabetes following mRNA vaccines (n=6) from Japan and Italy, with a smaller number of reports following Vaxzevria and inactivated COVID-19 vaccines. One study examined disproportionality in EudraVigilance of impaired glucose metabolism related PTs and found greater frequency with mRNA vaccines compared to adenovirus vector-based vaccines. • s33 [redacted]
Consistency of reporting	No other international regulator has updated their PI to include type 1 diabetes, and none are investigating this as a safety signal. The published case reports of type 1 diabetes following mRNA vaccines found in this TIP are all from Japan and Italy.
Quality of cases reported to the TGA	Overall, the fifteen Comirnaty reports submitted to the TGA were not of uniformly high standard. A causality assessment could not be performed for eight of the 15 reports due to insufficient information about time to onset (TTO). An additional case had TTO prior to vaccination. Of the six remaining reports, two were assessed as possible causality and four were assessed as probable causality (based on plausible TTO following vaccination and absence of alternative causes). All six reports appeared to have the diagnosis of type 1 diabetes verified, although only one was submitted by a health professional. Overall, the five Vaxzevria reports submitted to the TGA were of good quality. Although not submitted by health professionals, the diagnosis of type 1 diabetes appears verified for all five reports based on diagnosis and treatment in hospital. Based on the information provided, all five Vaxzevria reports can be considered to have probable causality given the plausible timing following vaccination and the absence of likely alternative causes. For reports associated with both vaccines, information on other possible triggers and autoantibody testing was generally lacking.
Characterisation of the risk/ clustering of reporting	For Comiranty, the age and sex distribution of reports is consistent with the epidemiology of background type 1 diabetes (e.g., higher reporting rate in 0-49 years compared to 50+ years and higher reporting rate in males compared to females). There was no clustering of reports with a particular dose number, with the reporting rate being similar after doses one, two and three plus.

	As there were only five Vaxzevria reports in total, analysis of age, gender and dose specific reporting rates is limited.
Temporal relationship	For the Comirnaty reports, no trend in the TTO could be identified. TTO was generally lacking, perhaps due to the vague nature of hyperglycaemic symptoms. Nine of 15 reports (60%) had unknown or non-specific TTO and one report had onset of symptoms prior to vaccination. The five remaining Comirnaty reports had TTOs of s22 respectively. For the Vaxzevria reports, four had definite TTO information. The average TTO for the four reports was s22 . The TTO of the five reports were s22 s22 respectively. There is possibly a trend in terms of all four reports having a time to onset of s22 or more, which is consistent with an autoimmune process. However, the small number of reports limits the analysis.
Specificity of the event	Autoimmune diseases, including type 1 diabetes, are thought to develop following environmental exposure in patients with genetic predisposition. SARS-CoV-2 infection is a possible environmental trigger, although this has not been proven. Information on SARS-CoV-2 infection and other possible infectious triggers for the cases reported to the TGA was generally lacking. Information on whether patients had autoimmune antibodies or a personal or family history of autoimmune diseases was also generally not provided.
Biological plausibility	Possible mechanisms for the development of type 1 diabetes following COVID-19 vaccination have been proposed but not proven. Sasaki et al, 2022 (in Diabetes and Metabolism) postulate two different mechanisms for beta-cell destruction in the pancreas, dependent upon the TTO between COVID-19 vaccination and the reported type 1 diabetes event. A shorter TTO (within seven days) associated with negative autoantibodies is suggestive of direct damage to beta cells by SARS-CoV-2 spike proteins or proinflammatory cytokines induced by COVID-19 vaccination. A longer TTO (four to seven weeks) and presence of autoantibodies suggests development of cross-immunity. In this scenario, vaccination of genetically predisposed patients could trigger autoimmunity if the presented viral antigen proteins are like beta-cell antigens. Another proposed mechanism discussed by Sasaki et al, 2022 (in J Diabetes Investig.) is that polyethylene glycol lipid conjugates contained in the COVID-19 mRNA vaccine might act as an adjuvant and induce autoimmune responses.
Health consequences	Type 1 diabetes can be life threatening in the short-term if not treated with insulin, due to the development of diabetic ketoacidosis (DKA). Both type 1 and type 2 diabetes are associated with long-term complications such as blindness, amputations, heart disease and kidney disease. If complications develop, diabetes can have a significant impact on quality of life and can reduce life expectancy. Patients with diabetes are at a high risk of adverse outcomes after COVID-19 infection, and infection itself can be associated with severe hyperglycaemia, including hyperglycaemic emergencies. Accordingly, ATAGI has identified patients with diabetes as a priority group for COVID-19 vaccination. None of the five Vaxzevria reports were admitted to ICU or had a fatal outcome. Four of the 15 Comirnaty cases (27%) were admitted to ICU or PICU with DKA. The age of these patients was 4 years, 8 years, 20 years and unknown, respectively. No reports had a fatal outcome.
Impact on clinical practice	If valid, practitioners should be informed that type 1 diabetes may occur in patients given COVID-19 vaccines. This would assist in early detection and may reduce the morbidity and mortality associated with DKA especially.
Concluding statement	Currently, there is insufficient evidence of a causal relationship between COVID-19 vaccines (Comirnaty and Vaxzevria) and type 1 diabetes. Although the TGA's DPAR identified disproportionate reporting for Comirnaty, an age adjusted OvE analysis showed significantly less cases than expected for both Comirnaty and Vaxzevria, the

	reporting rate is the same for both vaccines, no epidemiological studies of the risk of type 1 diabetes associated with COVID-19 vaccines were identified and no other regulator is investigating the signal or have updated their PIs. The cases reported to the TGA in association with Comirnaty were not of uniformly high quality, their age and gender distribution was consistent with the background epidemiology of type 1 diabetes and no trend in TTO or dose number was identified. Although the cases reported to the TGA in association with Vaxzevria were of a high quality and there was a possible trend in terms of TTO, there are too few to identify a trend in dose number, age or gender distribution. The signal can be returned to continued routine monitoring.

Priority

High

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

7:30pm, 4 September 2022: 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)*

Continue routine pharmacovigilance monitoring.

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)
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)
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
TTO	Time to onset

VERA	Vaccine Epidemiology and Rapid Assessment
VSIG	Vaccine Safety Investigation Group

s33 [redacted]

2. Vaccine information

Indication(s)	For 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). For COMIRNATY (BNT162b2 [mRNA]) COVID-19 Vaccine Pfizer: 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), 3 December 2021 (for 5 years and over), 17 January 2022 (booster dose for 16 to 17 years), and 8 April 2022 (booster dose for 12 to 15 years).
Vaccine roll-out status	**Australian Technical Advisory Group on Immunisations (ATAGI) recommendation for Comiranty** [26 July 2022 TRIM D22-5839194] The Comirnaty (Pfizer) vaccine is currently available as a: • first and second dose for people aged 5 years and older • third dose for people aged 5 years and older with severe immunocompromise • booster dose for people aged 16 years and older • fourth dose for people aged 30 years and older • fifth dose for people aged 16 years and older with severe immunocompromise, an underlying medical condition or disability. **ATAGI recommendation for Vaxzevria** [8 July 2022 TRIM D22-5839230] Vaxzevria (AstraZeneca) is approved for use in people aged 18 years and over. The TGA provisionally approved it for use in Australia on 15 February 2021. Pfizer, Moderna, or Novavax COVID-19 vaccines are preferred over AstraZeneca for people aged under 60 years. This is based on the higher risk and observed severity of a rare side effect called thrombosis with thrombocytopenia (TTS) after receiving AstraZeneca in people aged under 60 years compared with people aged 60 years or older. There is no brand preference for people aged 60 years and older. People aged 60 years or older are at higher risk of severe illness from COVID-19, meaning the benefits of vaccination outweigh the very small risk of TTS. AstraZeneca can be used in adults aged under 60 years if the person has made an informed decision based on an understanding of the risks and benefits. **Relevant ATAGI recommendation regarding Spikevax** [3 August 2022, TRIM D22-5839352] Following provisional approval of a new paediatric formulation of the Spikevax (Moderna) vaccine, the Australian Technical Advisory Group on Immunisation (ATAGI) have recommended COVID-19 vaccination for children

	aged 6 months to less than 5 years who are at increased risk of severe COVID-19. This includes children with: • a severely weakened immune system, such as those undergoing treatment for cancer, receiving immunosuppressive treatments or undergoing a bone marrow transplant • complex congenital cardiac disease • structural airway anomalies or chronic lung disease • **type 1 diabetes** • chronic neurological or neuromuscular conditions • a disability that requires frequent assistance, such as severe cerebral palsy or Down Syndrome.
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.

3. Adverse event information

Signal Source	The source of this TIP was the TGA May – June 2022 DPAR.
AESI status	There is no Brighton Collaboration Case Definition (BCCD) for Type 1 Diabetes Mellitus: *https://docs.google.com/spreadsheets/d/1QqF35nYcsaFN3DZTOtV_lP0TYqQzsDMUQBAd5M9brrM/edit#gid=1666959512* The TGA does not consider type 1 diabetes an adverse event of special interest (AESI) [TRIM D22-5152358]. It is not included in the Vaxzevria AESI list but is included in the Comirnaty AESI list [TRIM D22-5831017].
AEFI	Type 1 diabetes is an autoimmune condition in which the immune system is activated to destroy the cells in the pancreas which produce insulin. Without insulin, the body's cells cannot turn glucose (sugar), into energy. Treatment is directed toward managing the amount of sugar in the blood using insulin, diet and lifestyle to prevent complications. The exact cause is unknown, but it is believed to be the result of an interaction of genetic and environmental factors. The onset of type 1 diabetes is not linked to modifiable risk factors. Autoimmune diseases including type 1 diabetes, are thought to develop following environmental exposure in patients with genetic predisposition. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and vaccines against it could represent new environmental triggers for autoimmune endocrine disorders (Patrizio et al, 2021). Importantly, patients with diabetes are at a high risk of adverse outcomes after COVID-19 infection, and infection itself can be associated with severe hyperglycaemia, including hyperglycaemic emergencies (Ganakumar et al, 2022). Type 2 diabetes is a condition in which the body becomes resistant to the normal effects of insulin and gradually loses the capacity to produce enough insulin in the pancreas. The condition has strong genetic and family-related (non-modifiable) risk

factors and is also often associated with modifiable lifestyle risk factors. The exact genetic causes of type 2 diabetes are unknown.

Type 1 diabetes can be life threatening in the short-term if not treated with insulin, due to the development of diabetic ketoacidosis. Both type 1 and type 2 diabetes are associated with long-term complications such as blindness, amputations, heart disease and kidney disease. If complications develop, diabetes can have a significant impact on quality of life and can reduce life expectancy.
(https://www.diabetesaustralia.com.au/about-diabetes/what-is-diabetes/)

The clinical features at presentation that help to distinguish type 1 and type 2 diabetes are weight loss, ketonuria, time course, severity, family history and age. These are summarised in the table below, reproduced from Butler et al, 2022. Of note, type 1 diabetes peaks in pre-school and teenage years but can present at any age. Type 2 diabetes typically presents after the age of 40 but can present in younger patients.

Table 1 | Clinical features at presentation that help to distinguish type 1 and type 2 diabetes

	Type 1 diabetes	Type 2 diabetes
Weight loss	Yes (though not always, eg, in slow onset type 1)[1]	Unusual[1]
Ketonuria	Yes (though not always in slow onset type 1)[1]	No, unless patient has been fasting recently[1]
Time course for symptoms	Weeks or days[1]	Months to years[1]
Severity of symptoms (eg, nocturia >3x)	Often marked[1]	Variable, but usually not severe[1]
Family history	Possible family history of autoimmune disease[2] and/or insulin dependence at a young age[3]	Family history present in 30% with onset in adult life[4]
Age	Peak age in pre-school and teenage years, but can present at any age[5,6]	Typically after the age of 40, but can present in younger patients[5,6]

In patients with new onset hyperglycaemia where the type of diabetes is ambiguous, diabetes specific autoantibodies are the diagnostic test of choice to distinguish between type 1 and type 2 diabetes. Patients with newly diagnosed diabetes who are over 40 and respond well to oral anti-hyperglycaemic therapy do not need to undergo testing to distinguish between type 1 and type 2 diabetes. Glycated haemoglobin (HbA1c) is not recommended as a diagnostic test for patients with possible or suspected type 1 diabetes because it may not reflect a recent rapid rise in blood glucose and results take longer than with serum glucose testing.

Epidemiology
The overall incidence of type 1 diabetes in Australia in 2018 was 12 per 100,000 per year. The incidence is higher in males than females (14 and 10 per 100,000 per year). In general, the incidence is higher in younger age groups, peaking in the pre-school and teenage years. In Australia in 2018, the incidence in the 0-14 age group was 24 per 100,000, in the 15-24 age group was 18 per 100,000 and in the 25+ years age group was 7 per 100,000.

Magnitude of signal

TGA May-June 2022 DPAR

REACTION (PT)	PRR	TOTAL CASES
TYPE I DIABETES MELLITUS	3.35	17

This AEFI did not flag for any other COVID-19 vaccine pair.
Following DPAR, one of the Comirnaty cases was identified as a duplicate and another was identified as a Vaxzevria report, so there are 15 cases rather than 17.

Reporting Rate

Note that the analyses below all refer to reports coded with the PT 'Type 1 diabetes mellitus'. These were located in an AEMS search on 16 August 2022.

Reporting rate by vaccine overall

The table below shows that the overall Comirnaty and Vaxzevria reporting rates are similar. This was calculated based on a readjustment of the number of reports for Cimirnaty and Vaxzevria following review of the individual AEFI reports. One Comirnaty duplicate was removed and a Comirnaty report was reclassified as a Vaxzevria report.

VACCINE	TOTAL REPORTS	TOTAL DOSES**	TOTAL RR*
VAXZEVRIA	5	13844604	0.36
COMIRNATY	15	43652192	0.34

*RR= reporting rate per million doses

**Doses are from the TGA COVID-19 vaccine safety platform Qlik app, extracted on 16 August 2022.

Reporting rate by age group

The average age of the five Vaxzevria reports was 62 years with range of 46-75 years. The average age of the 14 Comiranty reports with known age was 26 years with a range of 8-63 years. The modal age was 32 years (n=4).

The table below shows that four of the five Vaxzevria reports were in the 50+ age group. However, the reporting rate is higher in the 0-49 age group as much fewer doses were administered to this age group than the 50+ age group. Comparing the Comirnaty age specific reporting rates with the Vaxzevria rates, the 0-49 age group rate is similar for both vaccines, but the 50+ age group rate is higher for Vaxzevria. The small number of Vaxzevria reports limits these comparisons. The increased reporting rate for both vaccines in the 0-49 age group compared to the 50+ age group is consistent with the epidemiology of background Type I Diabetes Mellitus.

VAXZEVRIA			
AGE	Reports	Doses**	RR*
0-49 YEARS	1	2379902	0.42
50+ YEARS	4	11464698	0.35
COMIRNATY			
AGE	Reports	Doses**	RR*
0-49 YEARS	13	28469395	0.46
50+ YEARS	1	15182791	0.07

*RR= reporting rate per million doses

**Doses are from the TGA COVID-19 vaccine safety platform Qlik app, extracted on 16 August 2022.

Reporting rate by gender

The table below shows that for Comirnaty, the reporting rate was higher in males than females. This is consistent with the epidemiology of background Type 1 Diabetes Mellitus. 67% of the Comirnaty reports were in males. For Vaxzevria, the reporting rate is higher in females than males, but the small number of reports limits the comparison. 60% of the Vaxzevria reports were in females.

VAXZEVRIA			
GENDER	Reports	Doses**	RR*
FEMALE	3	6836566	0.44
MALE	2	6980796	0.29
COMIRNATY			
GENDER	Reports	Doses	RR
FEMALE	5	22674433	0.22

MALE	10	20924954	0.48

*RR= reporting rate per million doses

**Doses are from the TGA COVID-19 vaccine safety platform Qlik app, extracted on 16 August 2022.

Reporting rate by dose number

The table below shows that for Comirnaty, the reporting rate is similar across doses one, two and three plus. For Vaxzevria, the reporting rate appears to decrease with subsequent dose numbers. However, the small number of reports limits this comparison.

VAXZEVRIA			
	Reports	**Doses****	**RR***
DOSE 1	3	6900968	0.43
DOSE 2	1	6814176	0.15
DOSE 3+	0	99216	0
COMIRNATY			
	Reports	**Doses****	**RR***
DOSE 1	5	14606234	0.34
DOSE 2	5	19056222	0.26
DOSE 3+	4	11733458	0.34

*RR= reporting rate per million doses

**Doses are from the Department of Health AIR COVID-19 Qlik app, extracted on 17 August 2022.

Time to onset analysis

For the Vaxzevria reports, four had definite TTO information. The average TTO for the four reports was s22 The TTO of the five reports were s22 , s22 respectively.

For the Comirnaty reports, TTO was generally lacking, perhaps due to the vague nature of hyperglycaemic symptoms. Nine of 15 reports (60%) had unknown or non-specific TTO and one report had onset of symptoms prior to vaccination. The five remaining Comirnaty reports had TTOs of s22 s22 respectively.

OvE analysis

Age stratified OvE analyses were performed for type 1 diabetes and Vaxzevria and Comirnaty.

Observed cases

Case definitions were not applied to observed cases and all reports with the PT 'Type 1 Diabetes Mellitus' were included. The AEMS search for cases to 16 August 2022 was used [TRIM D22-5796163].

Background rates and risk windows used

Incidence of type 1 diabetes was obtained from 2018 data from an Australian Institute of Health and Welfare (AIHW) analysis of National (insulin treated) Diabetes Register [TRIM D22-5838255 & TRIM D22-5796273]. The following age groups and rates were used in the OvE analysis:

Age group	**Incidence rate per 100,000 per year**
0-14 years	24
15-24 years	18
25+ years	7

A risk window of s22 was used as all cases (with known TTO) had a TTO within this time frame, and this is a biologically plausible time frame for the development of an auto-immune condition following vaccination. Cases with unknown TTO were included in the analysis.

Dose data

Doses administered of Comirnaty and Vaxzevria were obtained from the Australian Immunisation Register (AIR) (data processed through to 7 August 2022) [TRIM D22-5821995].

Results

The analyses are stored at TRIM D22-5796153. As shown in the table below, the number of observed cases of type 1 diabetes for both vaccines was significantly less than the age adjusted expected number of cases. Within the individual age strata, the observed was also significantly less than expected for both vaccines. For Vaxzevria, the OvE ratio was highest in the 25+ years age category (0.05) and for Comirnaty it was highest in the 0-14 years age category 0.04).

VAXZEVRIA

AGE GROUP	Observed cases	Expected cases	OvE ratio	LL 95% CI	UL 95% CI
0-14 YEARS	0	0.007	0	undefined	534.67
15-24 YEARS	0	10.62	0	undefined	0.35
25+ YEARS	5	107.30	0.05	0.02	0.11
TOTAL	5	117.93	0.04	0.01	0.10

COMIRNATY

AGE GROUP	Observed cases	Expected cases	OvE ratio	LL 95% CI	UL 95% CI
0-14 YEARS	4	106.07	0.04	0.01	0.10
15-24 YEARS	3	127.25	0.02	0.00	0.07
25+ YEARS	7	269.66	0.03	0.01	0.05
UNKNOWN	1				
TOTAL	15	502.98	0.03	0.02	0.05

No. and summary of AEFI reports

Summary of five Vaxzevria reports

Overall, the five Vaxzevria reports submitted to the TGA were of good quality. Although not submitted by health professionals, the diagnosis of type 1 diabetes appears verified for all five reports based on diagnosis in hospital and treatment of type 1 diabetes. Based on the information provided, all five Vaxzevria reports can be considered to have probable causality given the plausible timing following vaccination and the absence of likely alternative causes. Information on other possible triggers and autoantibody testing was generally lacking.

In terms of severity, none of the five Vaxzevria reports were admitted to ICU or had a fatal outcome.

s22

TGA ID	AGE, GENDER, JURISDICTION	TIME TO ONSET AND MANAGEMENT	DIAGNOSIS VERIFIED	CAUSALITY ASSESSMENT

	AND DOSE NUMBER		
606828	62 M, s22 s22	s22	Probable: s22
697605	71 F, s22 s22		Probable: s22
730653	57 F, s22 s22		Probable: s22
746741	75 F, s22 s22		Probable: s22
	s22		
714156	46 M, s22		Probable:

NB: THIS WAS INITIALLY RECORDED IN AEMS AS A COMIRNATY CASE	s22	s22

Summary of Comirnaty reports

Note that review of the Comirnaty cases revealed that one should have been coded as Vaxzevria (TGA ID 714156). This case was added to the table above of Vaxzevria cases. The reporting rates above were also recalculated.

Overall, the fifteen Comirnaty reports submitted to the TGA were of mixed quality, Eight of the 15 reports had insufficient information about TTO to enable a causality assessment. An additional case had TTO prior to vaccination. Of the six remaining reports, two were assessed as possible causality and four were assessed as probable causality (based on plausible TTO following vaccination and absence of alternative causes). All six reports appeared to have the diagnosis of type I diabetes verified, although only one was submitted by a health professional. Information on other possible triggers and autoantibody testing was generally lacking.

In terms of severity, four of the 15 cases (27%) were admitted to ICU or PICU. The age of these patients was s22, respectively. No reports had a fatal outcome.

TGA ID	AGE, GENDER, JURISDICTION AND DOSE NUMBER	TIME TO ONSET AND MANAGEMENT	DIAGNOSIS VERIFIED	CAUSALITY ASSESSMENT
725359	8 F, s22 s22	s22		Possible: s22 s22
699029	9 M, s22 s22			Unlikely: s22 s22

			s22	s22
	681145 NOTE THIS IS A DUPLICATE WITH 684762	12 M, s22 s22		Probable: s22 s22
	725232	14 F, s22 s22		Insufficient information provided
	630714	18 F, s22 s22		Insufficient information provided
	699843	20 M, s22 s22		Probable: s22 s22
	734490	20 M, s22 s22		Probable: s22 s22

	705750	31 F s22 s22	s22	Insufficient information provided
	668250	32 M, s22 s22		Insufficient information s22
	678427	32 M, s22 Dose unknown		Insufficient information s22
	681361	32 M, s22 s22		Probable: s22 s22
	726531	45 M, s22 s22		Insufficient information s22
	714156	This AEFI appears to be following Vaxzevria. ADR reports team notified and the AEFI has been added to the Vaxzevria table above.		
	724813	63 F s22 s22	s22	Insufficient information s22
	650026	32 M, from unknown S/T s22		Insufficient information s22
	726966	Male of unknown age from s22 s22		Possible: s22

4. Regulatory surveillance

Local, including:	**Product Information (PI)**

PI, Sponsor's PSUR/MSSR, and applicable clinical guidance	**Comirnaty PI** version pfpcobii10522, last updated 11 May 2022 Diabetes and changes in blood sugar levels are not described as adverse effects. **Vaxzevria PI** Doc ID-004490138 v17; last updated 25 July 2022 Diabetes and changes in blood sugar levels are not described as adverse effects.
	Applicable clinical guidance
	ATAGI information on contraindications and precautions for COVID-19 vaccines (last updated 21 February 2022) does not list diabetes. The advice on adverse reactions (last updated 4 March 2022) does not listed diabetes either.
	Sponsor's PSUR/MSSR/SSR
	Vaxzevria Periodic Safety Update Report 29 June 2021 – 28 December 2021 [TRIM D22-5242001] Type 1 diabetes is not identified as a safety concern. **Comirnaty Periodic Safety Update Report 19 December 2021 – 18 June** 2022 [TRIM D22-5831017] As type 1 diabetes is considered an AESI, an OvE analysis is provided in the PSUR (see pages 20, 24, 29, 32 & 44). These analyses include various risk windows and age stratified and adjusted. In all analyses, the observed number of reports is less than expected. Type 1 diabetes is not identified as a safety concern.
US FDA	**Label**
	Comirnaty drug label, last updated July 2022 Does not list diabetes or changes in blood sugar/ glucose level.
	Relevant regulatory action
	CDC Advisory Committee on Immunisation Practices (ACIP) vaccine recommendations *www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/covid-19.html* Diabetes is not identified as a safety concern in the 4 August 2022, 28 June 2022 or 17 March 2022 Morbidity and Mortality Weekly Reports. **Vaccines and Related Biological Products Advisory Committee** https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-june-28-2022-meeting-announcement Materials for the 28 June 2022 meeting were reviewed. Diabetes was not identified as a safety concern.
EU EMA	**Summary of Product Characteristics (SmPC)**
	Comirnaty SmPC – last updated 10 August 2022 Does not list diabetes or changes in blood sugar/ glucose level. **Vaxzevria SmPC** – last updated 12 August 2021 Does not list diabetes or changes in blood sugar/ glucose level.
	Relevant regulatory action

	EMA COVID-19 vaccines safety update, 3 August 2022 Diabetes is not identified as a safety concern. **EMA PRAC meeting highlights** 4-7 July 2022, 7-10 June 2022, 2-5 May 2022 Diabetes is not identified as a safety concern.
UK MHRA	**Summary of Product Characteristics (SPC)**
	Comirnaty SmPC, last updated 17 August 2022 Does not list diabetes or changes in blood sugar/ glucose level. **Vaxzevria SmPC,** last updated 1 July 2022 Dose not list diabetes or changes in blood sugar/ glucose level.
	Relevant regulatory action
	MHRA Coronavirus vaccine weekly summary of Yellow Card reporting, updated 4 August 2022 Diabetes is not identified as a safety concern.
Health Canada	**Product Monograph**
	Comirnaty product monograph, last revised 19 August 2022 Does not list diabetes or changes in blood sugar/ glucose level. **Vaxzevria product monograph**, last revised 5 May 2022 Does not list diabetes or changes in blood sugar/ glucose level.
	Relevant regulatory action
	Health Canada's COVID-19 vaccine weekly safety report – 5 August 2022 Diabetes is not identified as a safety concern.
NZ Medsafe	**Datasheet**
	Comirnaty datasheet, last revised 2 June 2022 Does not list diabetes or changes in blood sugar/ glucose level. **Vaxzevria product monograph**, last revised 4 April 2022 Does not list diabetes or changes in blood sugar/ glucose level.
	Relevant regulatory action
	Medsafe's weekly COVID-19 vaccine report, 30 June 2022 Diabetes is not identified as a safety concern.
Other international regulators (via ICMRA PV Network and ACCESS)	Diabetes was not identified as a safety concern at the following meetings of international regulators: **-European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) Meeting,** 18 – 21 July 2022 [TRIM D22-5723467] **-COVID-ETF (EMA's Pandemic Taskforce) Meeting,** Tuesday 14 July 2022 [TRIM D22-5697222] and Tuesday 14 June 2022 [TRIM D22-5584947] **-Access Consortium – COVID Vaccines & Therapeutics Working Group**, #28 Wednesday May 18th 2022 [TRIM D22-5578059] s 22 [redacted]

	s 22 [redacted]

5. Other information

s33 [redacted]

Literature	**PubMed search** Date: 23 August 2022 Search term: 'COVID-19 vaccine type 1 diabetes mellitus' Results: TRIM D22-5828069 **Overall summary** The published literature found in this search consisted mostly of case reports of type 1 diabetes following mRNA vaccines, with a smaller number of reports following Vaxzevria and inactivated COVID-19 vaccines. The case reports/ case series of new onset type 1 diabetes include eight patients aged 36 to 73. Six of the eight reports were following mRNA-based vaccines. Of these six reports, four followed dose 2 and two followed dose 1. One of the reports had an unspecified time to onset (TTO). Two had TTOs of two and three days respectively and three had TTOs of 28 days. Four of the six case reports are from Japan and two are from Italy. No formal epidemiological studies of the risk of type 1 diabetes associated with COVID-19 vaccines were found. One study examined disproportionality in EudraVigilance of impaired glucose metabolism related PTs and found greater frequency with mRNA vaccines compared to adenovirus vector-based vaccines. Some of the case reports discussed possible mechanisms for an association between COVID-19 vaccines and type 1 diabetes. For example, Sasaki et al, 2022 (in Diabetes and Metabolism) postulate two different mechanisms for beta-cell destruction in the pancreas, dependent upon the TTO between COVID-19 vaccination and the reported type 1 diabetes event. A shorter TTO (within seven days) associated with negative autoantibodies is suggestive of direct damage to beta cells by SARS-CoV-2 spike proteins or proinflammatory cytokines induced by COVID-19 vaccination. A longer TTO (four to seven weeks) and presence of autoantibodies suggests development of cross-

immunity. In this scenario, vaccination of genetically predisposed patients could trigger autoimmunity if the presented viral antigen proteins are like beta-cell antigens. Another proposed mechanism discussed by Sasaki et al, 2022 (in J Diabetes Investig) is that polyethylene glycol lipid conjugates contained in the COVID-19 mRNA vaccine might act as an adjuvant and induce autoimmune responses.

Case reports/ case series of new onset type 1 diabetes.

- 36-year-old female who developed type 1 diabetes with onset 3 days following dose 1 Comirnaty in Japan. She developed rapid onset DKA. Previously healthy with no history of diabetes, allergy or autoimmune disease. Islet-related autoantibodies were all negative. Human leukocyte antigen was haplotype DRB1*0405-DQB1*0401, which is associated with type 1 diabetes in Japan. The present case suggests that COVID-19 RNA-based vaccines might trigger the onset of type 1 diabetes, even in subjects without prior histories of diabetes. The authors do note that the as the patient's hyperglycaemic symptoms began only three days after vaccination, it is possible that the onset of type 1 diabetes merely coincided with the timing of COVID-19 vaccination. [Sakurai et al, 2022].
- 51-year-old female who developed type 1 diabetes with symptom onset 28 days after dose 1 Moderna in Japan. She received her 2nd dose of Moderna two days after symptom onset, and then her symptoms significantly worsened, although this was also accompanied by a daily intake of 1-2 litres of sugar- sweetened soda. Twelve days after the onset of symptoms she was hospitalised with acute onset DKA. She had a family history of type 2 diabetes but not of autoimmune disease. The patient was previously well with low-normal BMI, normal fasting glucose and HbA1C 45 days before first vaccination. Laboratory tests showed positive insulin autoantibody, and autoimmunity against the thyroid gland with normal levels of thyroid hormones. Immunological tests showed no evidence of a recent viral infection potentially triggering type 1 diabetes. Human leukocyte antigen (HLA) class II genotyping indicated DRB1*09:01-DQB1*03:03 homozygosity, which is known to confer susceptibility to type 1 diabetes in the Japanese population. The authors speculate *'…that COVID-19 mRNA vaccination triggered the development of type 1 diabetes in our patient, who had a genetic predisposition to the disease'* [Yano et al, 2022].
- 52-year-old male who developed Graves disease and type 1 diabetes with symptom onset 28 days after dose 2 of Comirnaty in Italy. The patient had a history of vitiligo vulgaris and an eight-year history of type 2 diabetes. No previous SARS-CoV-2 infection was documented. The conversion of pre-existing type 2 diabetes, into type 1 autoimmune diabetes, following the vaccine against SARS-CoV-2 was supported by positive islet-specific pancreatic autoantibodies (GAD65Ab) and very low levels of C-peptide, demanding a switch from oral antidiabetic therapy to insulin therapy to normalize the glycaemic profile [Patrizio et al, 2021].
- 50-year-old male who developed type 1 diabetes with symptom onset seven days after dose 1 of an inactivated COVID-19 vaccine, CoronaVac in China. He was diagnosed with fulminant type 1 diabetes with complete and irreversible islet destruction. He was previously healthy with a low-normal BMI and no family history of type 1 diabetes but his mother had type 2 diabetes. Autoantibodies were

negative but he was positive for the susceptibility human leukocyte antigen (HLA) alleles DQB1*02:03/03:03 and DRB1*09:01/09:01. t. The authors postulate that the patient did not have sufficient time to develop islet-associated antibodies given the sudden onset of the disease and that vaccination might evoke auto-immunity in individuals with susceptible genetic background and cause irreversible islet beta cell destruction and fulminant type 1 diabetes [Tang et al, 2022].

- 43-year-old male who developed type 1 diabetes with symptom onset two days after dose 2 of an unspecified mRNA COVID-19 vaccine in Japan. The patient had also been having monthly doses of nivolumab for malignant melanoma for 12 months, receiving the last dose seven days prior to the mRNA vaccination. The authors note that immune checkpoint inhibitors (ICI) such as nivolumab are associated with auto-immune diseases like type 1 diabetes but point out that this usually develops within seven months of treatment initiation. Also, during nivolumab treatment, his blood glucose level was tested every 4 weeks, and no increases were detected. Test results for islet-related autoantibodies were negative. They speculate that the mRNA vaccine administered before manifestation of hyperglycemic symptoms might have triggered fulminant onset of type 1 diabetes in this patient, who was at risk because of receiving ICI treatment (Sato et al, 2022).
- 73-year-old female who developed type 1 diabetes 28 days after dose 2 of Spikevax in Japan. She was strongly positive for autoantibodies and showed a disease-susceptible human leukocyte antigen haplotype, DRB1*04:05:01-DQB1*04:01:01. She had a history of mild glucose intolerance which had been treated with diet and exercise only for seven years. She had no family history of diabetes or autoimmune disease. The development of type 1 diabetes included a rise in her HbA1C four weeks after her 2nd Moderna vaccination and hyperglycaemia symptoms three weeks after this (Sasaki et al, 2022 in J Diabetes Investig).
- Two reports following Vaxzevria and Comirnaty in Italy (Bleve et al, 2022):
    - 57-year-old woman who developed type 1 diabetes with symptom onset 'a few days' after dose 1 of Vaxzevria. She had a family history of autoimmune diseases (vitiligo and Hashimoto thyroiditis) and type 2 diabetes. She a returned negative SARS-Cov-2 test. Anti-GAD, Anti-IA2, and Anti-TransGlut IgA autoantibodies were found.
    - 61-year-old woman developed type 1 diabetes with symptom onset 'since' dose 2 of Comirnaty. SARS-CoV-2 testing was negative. Anti-GAD and Anti-TPO autoantibodies were found. She reported a medical history of acquired hypothyroidism.

Case series of DKA in patients with pre-existing type 1 diabetes following COVID-19 vaccination:

- Two patients (20-year-old male and 25-year-old female) with pre-existing type 1 diabetes who developed severe DKA within a week of receiving dose 2 of Vaxzevria and Covaxin (inactivated whole virion) in India (Ganakumar et al, 2022).

Safety data base studies

This was a study of Individual Case Safety Reports (ICSRs) of impaired glucose metabolism events reported in the European database (Eudravigilance, EV).

	Reporting odds ratios (ROR) were computed to assess the reporting frequency for COVID-19 mRNA vaccines compared to COVID-19 viral vector-based vaccines. Overall, the most reported events were related to "high glucose levels" (2012; 47.06%). The mRNA vaccines were associated with an increased reporting frequency of "type 1 diabetes mellitus" (ROR 1.86; 95% CI 1.33-2.60), "type 2 diabetes mellitus" (ROR 1.58; 95% CI 1.03-2.42), "high glucose levels" (ROR 1.16; 95% CI 1.06-1.27), "diabetes mellitus inadequate control" (ROR 1.63; 95% CI 1.25-2.11), and "hypoglycemia" (ROR 1.62; 95% CI 1.41-1.86) compared to viral vector-based vaccines (di Mauro et al, 2022). **Literature discussing possible mechanisms** Sakurai et al 2022 discuss that the innate immune responses to viral infection accelerates aggressive β-cell destruction and is associated with the onset of fulminant Type 1 diabetes. Melanoma differentiation associated protein 5 (MDA5), is an innate pathogen recognition receptor. Because MDA5 regulates the innate immune response to SARS-CoV-2, it is likely that MDA5 recognizes RNA derived from COVID-19 RNA-based vaccines. Recognition of RNA by MDA5 induces the synthesis of type I interferons, which impair insulin production, proinsulin conversion and mitochondrial function in pancreatic β-cells. Patrizio et al 2021 discuss possible mechanisms for mRNA vaccine to induce autoimmune diseases such as autoimmune/inflammatory syndrome induced by adjuvants (ASIA syndrome), mRNA "self-adjuvant" effect, molecular mimicry between human and viral proteins and immune disruption from external stimuli. Sasaki et al, 2022 (in Diabetes and Metabolism] discuss that differences in time to onset (TTO) between COVID-19 vaccination and type 1 diabetes symptoms suggest different mechanisms for the beta-cell destruction. A shorter TTO (within seven days) associated with negative autoantibodies is suggestive of direct damage to beta cells by SARS-CoV-2 spike proteins or proinflammatory cytokines induced by COVID-19 vaccination. A longer TTO (four to seven weeks) and presence of autoantibodies suggests development of cross-immunity. In this scenario, vaccination of genetically predisposed patients could trigger autoimmunity if the presented viral antigen proteins are like beta-cell antigens. Bleve et al, 2022 postulate that the immune response triggered by COVID-19 vaccines leads to the production of pro-inflammatory cytokines, which play role in the pathogenesis of insulin-resistance and pancreatic beta-cell autoimmune damage. The increased circulating levels of these pro-inflammatory cytokines observed after vaccine might overlap an already imposed autoimmune process, exacerbating pancreatic beta-cell inflammation and contributing to clinically manifest diabetes.
Biological plausibility	**SARS-CoV-2 infection and hyperglycaemia** Proposed mechanisms include islet cell damage and acute insulinopenia after cellular entry via pancreatic ACE-2 receptor, cytokine storm, oxidative stress, overactivation of the renin-angiotensin-aldosterone system (RAAS), and dysregulated release of stress hormones like cortisol and catecholamines leading to increased insulin resistance [Ganakumar, et al, 2022]. **COVID-19 vaccines and type 1 diabetes** Sasaki et al, 2022 (in Diabetes and Metabolism) postulate two different mechanisms for beta-cell destruction in the pancreas, dependent upon the

	TTO between COVID-19 vaccination and the reported type 1 diabetes event. A shorter TTO (within seven days) associated with negative autoantibodies is suggestive of direct damage to beta cells by SARS-CoV-2 spike proteins or proinflammatory cytokines induced by COVID-19 vaccination. A longer TTO (four to seven weeks) and presence of autoantibodies suggests development of cross-immunity. In this scenario, vaccination of genetically predisposed patients could trigger autoimmunity if the presented viral antigen proteins are like beta-cell antigens. Another proposed mechanism discussed by Sasaki et al, 2022 (in J Diabetes Investig) is that polyethylene glycol lipid conjugates contained in the COVID-19 mRNA vaccine might act as an adjuvant and induce autoimmune responses.
s22	[redacted]

6. Conclusion

Conclusion	Currently, there is insufficient evidence of a causal relationship between COVID-19 vaccines (Comirnaty and Vaxzevria) and type 1 diabetes. The TGA's age adjusted OvE analysis showed significantly less cases than expected for both Comirnaty and Vaxzevria, the reporting rate is the same for both vaccines, no epidemiological studies of the risk of type 1 diabetes associated with COVID-19 vaccines were identified and no other regulator is investigating the signal or have updated their PIs. The cases reported to the TGA in association with Comirnaty were not of uniformly high quality, their age and gender distribution was consistent with the background epidemiology of type 1 diabetes and no trend in TTO or dose number was identified. Although the cases reported to the TGA in association with Vaxzevria were of a high quality and there was a possible trend in terms of TTO, there are too few to identify a trend in dose number, age or gender distribution. The signal can be returned to continued routine monitoring.	
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)
	Statement on validity/public health impact	
	N/A'	
	Specific instructions for selected regulatory action(s)	
	N/A	
Instructions for <Other> (if applicable)	N/A	

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Australian Government
Department of Health

Vaccines Surveillance Section (VSS) – Signal Investigation

TRIM reference:
D23-4058461

Comirnaty and Type I Diabetes Mellitus (second Signal Investigation)

Date and Time completed	5/12/2023 11:00 AM

Table of Contents

High-level summary 3
Executive summary 4
List of abbreviations 9
1. The vaccine(s) 10
Indications 10
Vaccine roll-out status 10
Mechanism of action 12
2. The adverse event(s) 12
AEFI 12
AESI status 14
3. The signal(s) 14
Signal Source 14
No. of AEFI reports 18
Report clustering and risk characterisation 19
Assessment of AEFI reports 21
Signal magnitude 24
s33 [redacted]
4. Literature 28
5. Regulatory surveillance 34
Australian regulatory surveillance 34
US FDA 35
EU EMA 35
UK MHRA 36
Health Canada 36
NZ Medsafe 36
Other international regulators 36
6. Impact 37
Impact on clinical practice 37
s22 [redacted] 37

Impact on other priority populations 38
7. Conclusion 38
Concluding statement, recommendations and rationale 38
Proposed action 39
Instructions for Stream B, MAVIS Evaluation Stream (if applicable) 39
Instructions for Stream C, ROS (if applicable) 39
Instructions for <Other> (if applicable) 39
References 39

High-level summary

The source of this Signal Investigation was a referral from the Pharmacovigilance Branch (PB) Principal Medical Advisor (PMA) [TRIM D23-3981730]. This vaccine-event pair was referred for a second Signal Investigation because of continued interest from a variety of stakeholders including Parliamentary Committees. s22 s22 (s22 The PB PMA recommended that the Signal Investigation focus on an updated literature review and consideration of the AEFI report #754141.

Type 1 diabetes is an autoimmune condition in which the immune system is activated to destroy the cells in the pancreas which produce insulin. Without insulin, the body's cells cannot turn glucose (sugar), into energy. The precise cause is unknown, but it is believed to be the result of an interaction of genetic and unknown environmental factors. The onset of type 1 diabetes is not linked to modifiable risk factors. Family history of a first degree relative with type 1 diabetes is the strongest risk factor, but 85% of those diagnosed do not have a family history. Age is another risk factor, with the incidence of type 1 diabetes peaking in the pre-school and teenage years. However, type 1 diabetes can develop at any age. Certain genetic HLA haplotypes (HLA DRB1-DQA1-DQB1) are known to confer type 1 diabetes risk (Maahs *et al.,* 2010). The overall incidence of type 1 diabetes in Australia in 2018 was 12 per 100,000 per year. The incidence is higher in males than females (14 versus 10 per 100,000 per year). The annual incidence in the 0-14 age group was 24 per 100,000, in the 15-24 age group was 18 per 100,000 and in the 25+ years age group was 7 per 100,000 (AIHW, 2022).

AEFI #754141 was reported to the TGA on s22 . The Evaluator notes that 3 of the 4 case reports in the associated s22 letter were reviewed in the first Signal Investigation and all 3 cases had a genetic predisposition to type 1 diabetes which was discussed by the authors. The remaining case report is reviewed in the Literature section of this current Signal Investigation. The long time to onset (s22) and apparent absence of genetic testing for this patient is noted. s22 s22

There have been 61 reports of possible new onset type 1 diabetes to the TGA's Adverse Event Monitoring System (AEMS) in association with COVID-19 vaccines. Of these, 41 were associated with Comirnaty, 14 with Vaxzevria, 5 with Spikevax and one with a non-specified trade name. None of the reports associated with Comirnaty or Spikevax had a fatal outcome.

Currently, there is insufficient evidence of a causal relationship between Comirnaty and new onset type 1 diabetes. Like the Sponsor's global observed versus expected (OvE) analyses, conservative age adjusted OvE analyses using Australian background incidence rates and reports in AEMS showed significantly less cases of type 1 diabetes than expected for Comirnaty overall and in the individual age strata. The overall TGA reporting rates of type 1 diabetes are similar for Comirnaty, Vaxzevria and Spikevax. Only one published epidemiological study with a control group was found that examined the risk of type 1 diabetes associated with Comirnaty, and this study (Xiong *et al.,* 2023) found no evidence of increased risk of incident diabetes following Comirnaty. No other regulator is investigating the signal or have updated their product information documents. Overall, of the sample examined, the reports of type 1 diabetes to the TGA in association with Comirnaty have low- medium quality and information about other possible risk factors was generally lacking. Their age and gender distribution (higher reporting rate in males and younger age groups) are consistent with the background epidemiology of type 1 diabetes and no trend in time to onset (TTO) was identified. s33 s33 s33 Taken

together with the greater use of Comirnaty (compared to other COVID-19 vaccines) in children, these results do not substantiate evidence of a causal association between Comirnaty and type 1 diabetes. There was not disproportionate reporting of type 1 diabetes in association with any COVID-19 vaccine in the recent TGA Disproportionality Analysis Report (DPAR). Given the current lack of evidence linking Comirnaty with the development of type 1 diabetes, the higher risk of SARS-CoV-2 infection in patients with type 1 diabetes, the demonstrated safety of vaccination in patients with diabetes, presently there is no overall benefit in alerting clinicians to a possible link between Comirnaty and type 1 diabetes through regulatory action. This signal can be returned to routine pharmacovigilance monitoring.

Executive summary

The vaccine(s)	The Australian Technical Advisory Group on Immunisation (ATAGI) identifies patients with diabetes mellitus requiring medication as being at increased risk of severe disease. Accordingly, it was recommended that these patients receive a 2023 COVID-19 vaccine dose. Comirnaty is the only COVID-19 vaccine currently registered for the 6 months to <5 age group and the 5 to <12 age group. In adolescents, Comirnaty and Spikevax are recommended. Thus, use of Comirnaty in the 0-19 age group is considerably higher than the use of other COVID-19 vaccines.
The adverse event(s)	Type 1 diabetes is an autoimmune condition in which the immune system is activated to destroy the cells in the pancreas which produce insulin. Without insulin, the body's cells cannot turn glucose (sugar), into energy. The precise cause is unknown, but it is believed to be the result of an interaction of genetic and unknown environmental factors. The onset of type 1 diabetes is not linked to modifiable risk factors. Family history of a first degree relative with type 1 diabetes is the strongest risk factor, but 85% of those diagnosed do not have a family history. Age is another risk factor, with the incidence of type 1 diabetes peaking in the pre-school and teenage years. However, type 1 diabetes can develop at any age. Certain genetic HLA haplotypes (HLA DRB1-DQA1-DQB1) are known to confer type 1 diabetes risk. The overall incidence of type 1 diabetes in Australia in 2018 was 12 per 100,000 per year. The incidence is higher in males than females (14 and 10 per 100,000 per year respectively). The annual incidence in the 0-14 age group was 24 per 100,000, in the 15-24 age group was 18 per 100,000 and in the 25+ years age group was 7 per 100,000.
The signal	**Signal source** The source of this Signal Investigation was a referral from the Pharmacovigilance Branch (PB) Principal Medical Advisor (PMA) [TRIM D23-3981730]. This vaccine-event pair was referred for a second Signal Investigation because of continued interest from a variety of stakeholders including Parliamentary Committees. s22 [redacted] It was recommended that the Signal Investigation focus on an updated literature review and consideration of the adverse event following immunisation (AEFI) report with TGA ID #754141. This AEFI was reported to the TGA on s22 [redacted]. The Evaluator notes that 3 of the 4 case reports in the s22 [redacted] letter were reviewed in the first Signal Investigation and all 3 cases had a genetic predisposition to type 1 diabetes which was discussed by the authors. The remaining case report is reviewed in the Literature section of this current Signal Investigation. The long time to onset (s22 [redacted]) and apparent absence of genetic testing for this patient is noted. s22 [redacted] **Number of AEFI reports** There have been 61 reports of possible new onset type 1 diabetes to the TGA's Adverse Event Monitoring System (AEMS) in association with COVID-19 vaccines. Of these, 41 were associated with Comirnaty, 14 with Vaxzevria, 5 with Spikevax and one with a non-

	specified trade name. None of the reports associated with Comirnaty or Spikevax had a fatal outcome.
	Report clustering and risk characterisation The age and gender distribution of the 27 Comirnaty reports to the TGA that describe new onset type 1 diabetes in the coding or case narrative is consistent with the background epidemiology of type 1 diabetes in Australia. The male reporting rate was higher than the female reporting rate. The 0-14 age group had the highest reporting rate, followed by the 15-24 age group. The 25+ age group had the lowest reporting rate. There is not a strong temporal relationship between Comirnaty and reports of type 1 diabetes, as there was not an apparent trend in the time to onset (TTO) of reports. There is an apparent trend in the dose specific reporting rates, with the reporting rate of type 1 diabetes associated with Comirnaty highest with dose 1 and decreasing with subsequent doses. Taken together, these findings are not supportive of a causal relationship between Comirnaty and type 1 diabetes.
	Assessment of AEFI reports Of the 10 AEFI reports reviewed in this current Signal Investigation, diagnostic certainty was medium in 90% and high in 10%, although none of the reports had a health professional as their primary source. Causality was un-assessable in 40% of reports due to insufficient information about time to onset, possible in 50% and unlikely in 10%. None of the 10 AEFI reports to the TGA describe the results of any genetic testing. Family history was absent in 30% of reports and not described in 70% of reports. Overall, the reports have low-medium quality. Information about other possible causes/ triggers/ risk factors was generally lacking.
	Signal magnitude The overall TGA reporting rates of type 1 diabetes are similar for Comirnaty, Vaxzevria and Spikevax, ranging from 0.09 to 0.10 reports per 100,000 doses. An observed versus expected (OvE) analysis using Australian background incidence rates and reports in AEMS was conducted. It was a sensitive analysis as case definitions were not applied to observed cases, all reports with the PTs 'Type 1 diabetes mellitus', 'Diabetes mellitus' and 'Diabetic ketoacidosis' were included and cases with unknown time to onset were not excluded. The number of observed cases of type 1 diabetes for both Comirnaty and Vaxzevria were significantly less than the age adjusted expected number of cases (e.g., the Comirnaty OvE ratio was 0.10 with a 95% confidence internal of 0.07-0.13). Within the individual age strata, the observed number was also significantly less than expected for both vaccines. There was not disproportionate reporting to the TGA of type 1 diabetes or DKA in association with any COVID-19 vaccines in the September-October 2023 disproportionality analysis report (DPAR). Taken together, these quantitative findings are not supportive of a causal association between Comirnaty and type 1 diabetes.
	s33 [redacted]
Literature	Taken together with the findings from the literature review in the first signal investigation, only one published epidemiological study with a control group was found that examined the risk of type 1 diabetes associated with Comirnaty, and this study

	(Xiong et al., 2023) found no evidence of increased risks of incident diabetes following Comirnaty. In the published case reports and series, there is a preponderance of reports following mRNA vaccines but the Evaluator notes that this may represent greater use of mRNA vaccines globally, as reporting rates of type 1 diabetes to the TGA are similar for Comirnaty and Vaxzevria. In addition, approximately 50% occurred in individuals with type 1 susceptibility, according to human leukocyte antigen (HLA) typing (Lin et al., 2023). The Evaluator notes that of those without identified genetic susceptibility, whether genetic testing was undertaken is often not stated. The case reports and series have a very wide range of time to onsets. Similar to the finding from the first Signal Investigation, most of the case reports/ series were from Japan and Italy. Alsudais et al., 2023 found a small number of new-onset diabetes cases coincidently occurring soon after the COVID-19 vaccine, especially in those with genetic susceptibility. Despite being older, these patients had a similar phenotype to traditional type 1 diabetes. Overall, the literature findings are not supportive of a causal association between Comirnaty and type 1 diabetes.
Biological plausibility	No association between non-COVID-19 immunisations and islet autoimmunity or type 1 diabetes has been found thus far. A meta-analysis reviewed 23 studies investigating 16 vaccinations and analyzed 11 studies that met the inclusion criteria (Morgan et al., 2016). Overall, there was no evidence to suggest an association between any of the childhood vaccinations investigated and type 1 diabetes. Mechanisms for COVID-19 vaccines to cause type 1 diabetes have been proposed such as molecular mimicry-related cross-reactivity between SARS-CoV-2 antigens and receptors involved in autoimmunity or autoimmune/inflammatory syndrome induced by adjuvants (Lin et al., 2023). A specific mechanism for mRNA vaccines has been proposed, involving a protein called MDA5 (Guo et al., 2023). These mechanisms have not been proven however, and Guo et al., 2023 conclude that further exploration is necessary to establish a causal relationship between COVID-19 vaccines and autoimmune diseases such as type 1 diabetes.
Australian regulatory surveillance	Type 1 diabetes is not listed as an adverse event in the Australian Product Information documents for any COVID-19 vaccines, nor in the Australian Immunisation Handbook. Patients with diabetes requiring insulin treatment are identified by the Australian Technical Advisory Group as being at increased risk of severe COVID-19 infection. The TGA's Risk Management Section (RMS) conducted a review of the Sponsor's 6-month Periodic Safety Update Report (PSUR) for Comirnaty, covering the period 19 December 2022 through 18 June 2023: D23-3277505. Diabetes was not identified as a safety concern. Appendix 5.8 of the Sponsor's PSUR contains OvE analyses for adverse events of special interest. Type 1 diabetes is considered an AESI. In overall and age stratified OvE analyses, the observed number of reports of type 1 diabetes in association with Comirnaty globally is less than expected based on the background incidence of type 1 diabetes.
International regulatory surveillance	No other regulator is investigating the signal of Comirnaty and type 1 diabetes or have updated their product information documents to include it as an adverse event.
Impact on clinical practice	The severity of type 1 diabetes is acknowledged, especially diabetic ketoacidosis (DKA), which is a frequent presentation. However, given the current lack of evidence linking Comirnaty with the development of type 1 diabetes, the higher risk of SARS-CoV-2 infection in patients with type 1 diabetes, the demonstrated safety of vaccination in patients with diabetes, presently there is no overall benefit in alerting clinicians to a possible link between Comirnaty and type 1 diabetes through regulatory action.
s22 [redacted]	
Concluding statement,	Currently, there is insufficient evidence of a causal relationship between Comirnaty and new onset type 1 diabetes. Like the Sponsor's global OvE analyses, conservative age

recommendations and rationale	adjusted OvE analyses using Australian background incidence rates and reports in AEMS showed significantly less cases of type 1 diabetes than expected for Comirnaty. The overall TGA reporting rates of type 1 diabetes are similar for Comirnaty, Vaxzevria and Spikevax. Only one published epidemiological study with a control group was found that examined the risk of type 1 diabetes associated with Comirnaty, and this study (Xiong et al., 2023) found no evidence of increased risks of incident diabetes following Comirnaty. No other regulator is investigating the signal or have updated their PIs. Overall, of the sample examined, the reports of type 1 diabetes to the TGA in association with Comirnaty are low- medium quality and information about other possible risk factors is generally lacking. Their age and gender distribution (higher reporting rate in males and younger age groups) are consistent with the background epidemiology of type 1 diabetes and no trend in TTO was identified. s33 [redacted] s33 [redacted] s33 [redacted] Comirnaty (compared to other COVID-19 vaccines) in children, these results do not substantiate evidence of a causal association between Comirnaty and type 1 diabetes. There was not disproportionate reporting to the TGA of type 1 diabetes or DKA in association with any COVID-19 vaccines in the recent DPAR report. Given the current lack of evidence linking Comirnaty with the development of type 1 diabetes, the higher risk of SARS-CoV-2 infection in patients with type 1 diabetes, the demonstrated safety of vaccination in patients with diabetes, presently there is no overall benefit in alerting clinicians to a possible link between Comirnaty and type 1 diabetes through regulatory action. This signal can be returned to routine pharmacovigilance monitoring.

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

<Type your decision in this box, then delete all italicised text below>

Include the date and time of this review.

Provide a comment on the proposed recommendations for this V-E pair, e.g.:

- *The MO5/Stream Lead endorses the recommendations outlined above (unchanged), OR*
- *Given consideration to additional factors (e.g. Staff resourcing, program resources), the MO5 recommends the following…*

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)

<Type your recommendations in this box (in bold), then delete all italicised text below>

Make a recommendation, based on the available data, whether to progress to the one of the following:

- *Return to routine monitoring*

- *If your AEFI is an AESI, then the following wording can be used: "Continue to monitor through routine enhanced pharmacovigilance processes for AESIs, including weekly review of reporting rates and O/E analyses."*
  (NB – there are some AESIs for which we are not doing weekly O/E analyses because we do not have the background rates for them. This can be checked by referring to E20-348819)
- *If your AEFI is NOT an AESI the following wording can be used: "Continue routine pharmacovigilance monitoring"*

- *Referral to MAVIS evaluation stream for signal investigation.*
- *Referral for expert advice*
  - *Referral to Regulatory Outcomes Stream (ROS) to risk minimisation activity (be specific if possible, such as PI update, web statement, Dear Healthcare Professional Letter, provider education, fridge stickers, patient alert card, addition to Monthly Safety Summary Reports, update to RMP Australian Specific Annexe, etc.).* ***NB: Please provide a copy of PCDs of relevant case reports (save to TRIM) to assist ROS in negotiating with the sponsor.***
  - *Escalate to PSAB Branch Head and above at earliest opportunity (for example, if VSIG criteria are met – see TRIM D21-2140941)*
  - *Request further information from jurisdictional immunisation coordinator (JIC) regarding individual cases if this is required to reach a conclusion and make a recommendation.*
- *If brief additional information has been requested, this may be included at the end of this report as an addendum. For example: "The requested additional information regarding CASE X has been provided. Based on this data, there are no changes to the overall conclusion and recommendation of this report. OR Based on this data, it is recommended that a subsequent review is commenced to investigate Y" (in which case a new report would also then be opened).*

If a significant amount of information has been requested, a new, subsequent review should be commenced.

Priority

High

Assign the priority as Low, Medium, or High. Clicking within the bolded text will reveal a drop-down box.

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 the 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). These issues are more pronounced in Signal Investigations with large numbers (e.g., greater than 30 AEFI reports per vaccine) as it is not feasible to review the case narratives for each AEFI and confirm coded information such as dose number and time to onset against this information in the case narrative.

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.

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)
CMI	Consumer Medicine Information
COVID-19	Coronavirus disease 2019
DHCPL	Dear Healthcare Professional Letter
DM	Diabetes Mellitus
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)
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
SI	Signal Investigation
SPC/SmPC	Summary of Product Characteristics
SSR	Safety Summary Report
STRS	Surveillance and Targeted Review Stream
TIP	Targeted Investigation Process
TTO	Time to onset
VERA	Vaccine Epidemiology and Rapid Assessment
VSIG	Vaccine Safety Investigation Group

s33

1. The vaccine(s)

Indications	For 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). For 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). For 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). For 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).
Vaccine roll-out status	**Information about COVID-19 vaccines from the Australian Immunisation Handbook** (last updated 27 November 2023, TRIM D23-4351792) The Australian Technical Advisory Group on Immunisation (ATAGI) identifies patients with diabetes mellitus requiring medication as being at increased risk of severe disease. Accordingly, it was recommended that these patients receive a 2023 COVID-19 vaccine dose. Recommendations for infants, children and adolescents **Children aged 6 months to <5 years** are recommended to receive COVID-19 vaccine if they have severe immunocompromise, disability or complex/multiple health conditions that increase their risk of severe COVID-19. Children aged 6 months to <5 years are recommended to receive COVID-19 vaccine in a 3-dose schedule, with each dose 8 weeks apart. Comirnaty Original is the only formulation currently registered for this age group. **Children aged 5 – <12 years** are recommended to receive COVID-19 vaccines. Primary course vaccination is recommended for all children aged 5 - <12 years. The recommended schedule is 2 doses, 8 weeks apart. An additional (3rd) primary dose is recommended for severely immunocompromised children, which should be given 8 weeks after the second dose. After completing a primary course, a 2023 dose can be considered for children aged 5 -<12 years who have medical comorbidities that increase their risk of severe COVID-19 or disability with significant or complex health needs, and whose last COVID-19 vaccine dose was 6 months ago or longer. Omicron XBB.1.5-based vaccines are preferred for the primary course and for further doses in this age group. Children aged 5 - <12 years can receive Comirnaty Omicron XBB.1.5 5 - <12 years formulation (light blue cap). **Adolescents aged 12 - <18 years** are recommended to receive COVID-19 vaccines. Primary course vaccination is recommended for all adolescents aged 12 – <18 years. The recommended schedule for the primary course is 2 doses, 8 weeks apart. An additional (3rd)

primary course dose is recommended for severely immunocompromised adolescents, which should be given 8 weeks after the second dose.

After completing a primary course, a 2023 dose can be considered for adolescents who have medical comorbidities that increase their risk of severe COVID-19 or disability with significant or complex health needs, and whose last COVID-19 vaccine dose was 6 months ago or longer.

Omicron XBB.1.5-based vaccines are preferred for the primary course and for further doses in this age group. People aged ≥12 years can receive Comirnaty Omicron XBB.1.5 ≥12 years formulation (dark grey cap) and Spikevax Omicron XBB.1.5. Comirnaty bivalent Original/Omicron BA.4/5, Spikevax bivalent Original/Omicron BA.4/5, and Nuvaxovid Original can also be used for primary or further doses but are not preferred.

Examination of vaccine doses reported to the Australian Immunisation Register (AIR) in the 0-19 age group.
Below are doses of vaccine reported to the AIR in different age groups by trade name, to 31 October 2023 [Source, TRIM D23-3934955].

AGE	VAXZEVRIA	COMIRNARTY	SPIKEVAX	NUVAXOVID	SPIKEVAX_BIVALENT	COMINARTY_BIVALENT1	COMINARTY_BIVALENT45	SPIKEVAX_BIVALENT45
19 & UNDER	119,284	6,960,861	484,542	8,936	5,494	7,080	29,443	9,282
20-29	844,115	6,954,963	692,891	36,344	28,102	31,414	88,277	34,421
30-39	895,562	8,052,444	811,726	51,831	69,204	42,668	127,748	50,770
40-49	605,875	7,732,930	740,554	45,888	80,363	48,009	162,136	62,208
50-59	2,299,347	6,110,851	904,646	46,943	124,137	83,934	284,777	120,984
60-69	4,164,496	3,873,667	975,717	45,538	160,971	171,817	509,565	199,278
70-79	3,305,208	3,106,586	630,579	28,838	131,538	231,364	574,595	170,140
80+	1,623,820	1,976,837	288,807	11,547	67,432	136,842	350,007	90,067
UNKNOWN	4	8	-	-	-	-	1	-

Combining the different Comirnaty and Spikevax formulations, the table below provides the combined doses for the different Sponsors in the 0-19 age group. It shows for example that in Australia, the number of Comirnaty doses given to 0–19-year-olds is 59 times greater than Vaxzevria, 14 times greater than Spikevax and 783 times greater than Nuvaxovid.

	ALL COMIRNATY	ALL SPIKEVAX	VAXZEVRIA	NUVAXOVID
0-19	6,997,384	499,318	119,284	8,936

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. 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).
Summary of 'vaccine(s)' section	The Australian Technical Advisory Group on Immunisation (ATAGI) identifies patients with diabetes mellitus requiring medication as being at increased risk of severe disease. Accordingly, it was recommended that these patients receive a 2023 COVID-19 vaccine dose. Comirnaty is the only COVID-19 vaccine currently registered for the 6 months to <5 age group and the 5 to <12 age group. In adolescents, Comirnaty and Spikevax are recommended. Thus, use of Comirnaty in the 0-19 age group is considerably higher than the use of other COVID-19 vaccines.

2. The adverse event(s)

AEFI	Type 1 diabetes is an autoimmune condition in which the immune system is activated to destroy the cells in the pancreas which produce insulin. Without insulin, the body's cells cannot turn glucose (sugar), into energy. The exact cause is unknown, but it is believed to be the result of an interaction of genetic and environmental factors. The onset of type 1 diabetes is not linked to modifiable risk factors. Autoimmune diseases including type 1 diabetes, are thought to develop following environmental exposure in patients with genetic predisposition. It has been proposed that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and vaccines against it could represent new environmental triggers for autoimmune endocrine disorders (Patrizio *et al.,* 2021). Importantly, patients with diabetes are at a high risk of adverse outcomes after COVID-19 infection, and infection itself can be associated with severe hyperglycaemia, including hyperglycaemic emergencies (Ganakumar *et al.*, 2022). The majority of cases are attributable to an autoimmune-mediated destruction of beta cells (type 1a) while a small minority of cases results from an idiopathic destruction or failure of beta cells (type 1b) (Maahs *et al.,* 2010). Fulminant type 1 diabetes is a subtype of type 1 diabetes characterized by severe progression of hyperglycemia to ketoacidosis without a significant increase in glycated hemoglobin (HbA1c) levels, typically in a short period (within a week). Additionally, depletion of insulin secretion has been confirmed in patients with fulminant type 1 diabetes. Interestingly, islet-related autoantibodies are absent in most patients with fulminant type 1 diabetes. Risk factors for type 1 diabetes include [TRIM D23-4099059 & D23-4099417]:

1. Family history: anyone with a parent, sibling or child with type 1 diabetes has a 15-fold higher risk of developing the condition. **However, nearly 85% of diagnoses occur in people who have no family members with the disease** [TRIM D23-4099417]. Family history is more common in childhood-onset type 1 diabetes than adult-onset type 1 diabetes (Maahs *et al*., 2010).
2. Genetics: certain HLA haplotypes (HLA DRB1-DQA1-DQB1) are known to confer type 1 diabetes risk. Although 90–95% of young children with T1D carry either or both susceptibility haplotypes, approximately 5% or fewer persons with HLA-conferred genetic susceptibility actually develop clinical disease (Maahs *et al.,* 2010).
3. Other autoimmune diseases such as autoimmune thyroid disease, Addison's disease, celiac disease, and autoimmune gastritis.
4. Age: type 1 diabetes can occur at and age, but it appears to have 2 noticeable peaks. The first peak occurs in children between 4 and 7 years old and the second is in children between 10 and 14 years old.
5. Unknown environmental triggers: Research has not found a definite environmental trigger for type 1 diabetes. Viruses and exposure to gluten, cow's milk, antibiotics, and more have all been extensively studied.
6. Ethnic and geographic triggers: the number of people who have type 1 diabetes tends to be higher as you travel away from the equator. The risk for type 1 diabetes has historically been highest in those with white European ancestry. However, the diversity of the population with T1D is increasing, meaning the risk is going up in minority populations

Type 2 diabetes is a condition in which the body becomes resistant to the normal effects of insulin and gradually loses the capacity to produce enough insulin in the pancreas. The condition has strong genetic and family-related (non-modifiable) risk factors and is also often associated with modifiable lifestyle risk factors. The exact genetic causes of type 2 diabetes are unknown.

Treatment of type 1 diabetes is directed toward managing the amount of sugar in the blood using insulin, diet and lifestyle to prevent complications. Type 1 diabetes can be life threatening in the short-term if not treated with insulin, due to the development of diabetic ketoacidosis. Both type 1 and type 2 diabetes are associated with long-term complications such as blindness, amputations, heart disease and kidney disease. If complications develop, diabetes can have a significant impact on quality of life and can reduce life expectancy. (https://www.diabetesaustralia.com.au/about-diabetes/what-is-diabetes/)

The clinical features at presentation that help to distinguish type 1 and type 2 diabetes are weight loss, ketonuria, time course, severity, family history and age. These are summarised in the table below, reproduced from Butler et al, 2022. Of note, type 1 diabetes peaks in childhood and adolescence but can present at any age. Type 2 diabetes typically presents after the age of 40 but can present in younger patients.

Table 1 | Clinical features at presentation that help to distinguish type 1 and type 2 diabetes

	Type 1 diabetes	Type 2 diabetes
Weight loss	Yes (though not always, eg, in slow onset type 1)[1]	Unusual[1]
Ketonuria	Yes (though not always in slow onset type 1)[1]	No, unless patient has been fasting recently[1]
Time course for symptoms	Weeks or days[1]	Months to years[1]
Severity of symptoms (eg, nocturia >3x)	Often marked[1]	Variable, but usually not severe[1]
Family history	Possible family history of autoimmune disease[2] and/or insulin dependence at a young age[3]	Family history present in 30% with onset in adult life[4]
Age	Peak age in pre-school and teenage years, but can present at any age[5,6]	Typically after the age of 40, but can present in younger patients[5,6]

	In patients with new onset hyperglycaemia where the type of diabetes is ambiguous, diabetes specific autoantibodies are the diagnostic test of choice to distinguish between type 1 and type 2 diabetes. Patients with newly diagnosed diabetes who are over 40 and respond well to oral anti-hyperglycaemic therapy do not need to undergo testing to distinguish between type 1 and type 2 diabetes. Glycated haemoglobin (HbA1c) is not recommended as a diagnostic test for patients with possible or suspected type 1 diabetes because it may not reflect a recent rapid rise in blood glucose and results take longer than with serum glucose testing. **Epidemiology** The overall incidence of type 1 diabetes in Australia in 2018 was 12 per 100,000 per year. The incidence is higher in males than females (14 and 10 per 100,000 per year). In general, the incidence is higher in younger age groups, peaking in the pre-school and teenage years, but it can develop at any age. In Australia in 2018, the incidence in the 0-14 age group was 24 per 100,000, in the 15-24 age group was 18 per 100,000 and in the 25+ years age group was 7 per 100,000.
AESI status	There is no Brighton Collaboration Case Definition (BCCD) for Type 1 Diabetes Mellitus: *https://docs.google.com/spreadsheets/d/1QqF35nYcsaFN3DZTOtV_lP0TYqQzsDMUQBAd5M9brrM/edit#gid=1666959512* The TGA does not consider type 1 diabetes an adverse event of special interest (AESI) for COVID-19 vaccines [TRIM D22-5152358]. It is not included in the Vaxzevria AESI list but is included in the Comirnaty AESI list [TRIM D22-5831017].
Summary of 'adverse event(s)' section	Type 1 diabetes is an autoimmune condition in which the immune system is activated to destroy the cells in the pancreas which produce insulin. Without insulin, the body's cells cannot turn glucose (sugar), into energy. The precise cause is unknown, but it is believed to be the result of an interaction of genetic and unknown environmental factors. The onset of type 1 diabetes is not linked to modifiable risk factors. Family history of a first degree relative with type 1 diabetes is the strongest risk factor, but 85% of those diagnosed do not have a family history. Age is another risk factor, with the incidence of type 1 diabetes peaking in the pre-school and teenage years. However, type 1 diabetes can develop at any age. Certain genetic HLA haplotypes (HLA DRB1-DQA1-DQB1) are known to confer type 1 diabetes risk. The overall incidence of type 1 diabetes in Australia in 2018 was 12 per 100,000 per year. The incidence is higher in males than females (14 and 10 per 100,000 per year respectively). The annual incidence in the 0-14 age group was 24 per 100,000, in the 15-24 age group was 18 per 100,000 and in the 25+ years age group was 7 per 100,000.

3. The signal(s)

Signal Source	The source of this Signal Investigation was a referral from the Pharmacovigilance Branch (PB) Principal Medical Advisor (PMA) [TRIM D23-3981730]. This vaccine-event pair was referred for a second Signal Investigation because of continued interest from a variety of stakeholders including Parliamentary Committees. s22 [redacted] s22 [redacted] s22 [redacted] The PB PMA recommended that the Signal Investigation focus on an updated literature review and consideration of the AEFI report TGA ID #754141. This AEFI was first reported to the TGA on s22 [redacted]

The previous Signal Investigation considered Type I Diabetes Mellitus in association with Comirnaty and Vaxzevria [TRIM D22-5794110]. It was completed on 30 August 2022. The conclusion from this Signal Investigation was:

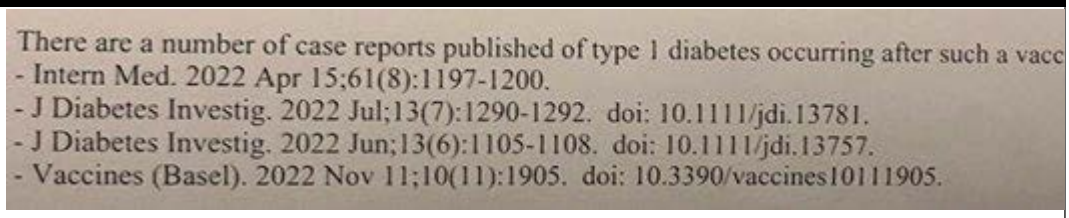
Currently, there is insufficient evidence of a causal relationship between COVID-19 vaccines (Comirnaty and Vaxzevria) and type 1 diabetes. The TGA's age adjusted OvE analysis showed significantly less cases than expected for both Comirnaty and Vaxzevria, the reporting rate is the same for both vaccines, no epidemiological studies of the risk of type 1 diabetes associated with COVID-19 vaccines were identified and no other regulator is investigating the signal or have updated their PIs. The cases reported to the TGA in association with Comirnaty were not of uniformly high quality, their age and gender distribution was consistent with the background epidemiology of type 1 diabetes and no trend in TTO or dose number was identified. Although the cases reported to the TGA in association with Vaxzevria were of a high quality and there was a possible trend in terms of TTO, there are too few to identify a trend in dose number, age or gender distribution. The signal can be returned to continued routine monitoring.

Details about AEFI #754141:

AGE/ GENDER/ JURISDICTION	VACCINATION DATE	SYMPTOM ONSET DATE	TTO	OUTCOME	FAMILY HISTORY	OTHER INFORMATION
35 F, s22	s22					

s22

s22 [redacted]


There are a number of case reports published of type 1 diabetes occurring after such a vacc
- Intern Med. 2022 Apr 15;61(8):1197-1200.
- J Diabetes Investig. 2022 Jul;13(7):1290-1292. doi: 10.1111/jdi.13781.
- J Diabetes Investig. 2022 Jun;13(6):1105-1108. doi: 10.1111/jdi.13757.
- Vaccines (Basel). 2022 Nov 11;10(11):1905. doi: 10.3390/vaccines10111905.

1. Yano M, Morioka T, Emoto M, et al. New-onset Type 1 Diabetes after COVID-19 mRNA Vaccination. *Intern Med 2022*; 61(8): 1197-1200. [TRIM D22-5825455]
2. Sakurai K, Narita D, Saito N, et al. Type 1 diabetes mellitus following COVID-19 RNA-based vaccine. *J Diabetes Investig 2022;* 13(7): 1290-1292. [TRIM D22-5823484]
3. Sasaki H, Itoh A, Watanabe Y, et al. Newly developed type 1 diabetes after coronavirus disease 2019 vaccination: A case report. *J Diabetes Investig 2022*; 13(6): 1105-1108. [TRIM D22-5825764]
4. Lin R, Lin YW, Chen MH. Fulminant Type 1 Diabetes Mellitus after SARS-CoV-2 Vaccination: A Case Report. *Vaccines (Basel) 2022*; 10(11): 1905. TRIM D23-4278833.

The first 3 case reports were reviewed in the first Comirnaty/ Vaxzevria and type 1 diabetes Signal Investigation. It is noted that all 3 cases had a genetic predisposition to type 1 diabetes which was discussed by the authors. The following assessments were made at the time of the first Signal Investigation:

- Yano *et al.,* 2022: 51-year-old female who developed type 1 diabetes with symptom onset 28 days after dose 1 Spikevax in Japan. She received her 2nd dose of Spikevax 2 days after symptom onset, and then her symptoms significantly worsened, although this was also accompanied by a daily intake of 1-2 litres of sugar- sweetened soda… Laboratory tests showed positive insulin autoantibody, and autoimmunity against the thyroid gland with normal levels of thyroid hormones. Immunological tests showed no evidence of a recent viral infection potentially triggering type 1 diabetes. Human leukocyte antigen (HLA) class II genotyping indicated DRB1*09:01-DQB1*03:03 homozygosity, which is known to confer susceptibility to type 1 diabetes in the Japanese population. The authors speculate '*…that COVID-19 mRNA vaccination triggered the development of type 1 diabetes in our patient, who had a genetic predisposition to the disease'*.
- Sakurai *et al.,* 2022: 36-year-old female who developed type 1 diabetes with onset 3 days following dose 1 Comirnaty in Japan… Previously healthy with no history of diabetes, allergy or autoimmune disease. Islet-related autoantibodies were all negative. Human leukocyte antigen was haplotype DRB1*0405-DQB1*0401, which is

	associated with type 1 diabetes in Japan. The present case suggests that COVID-19 RNA-based vaccines might trigger the onset of type 1 diabetes, even in subjects without prior histories of diabetes. The authors do note that the as the patient's hyperglycaemic symptoms began only three days after vaccination, it is possible that the onset of type 1 diabetes merely coincided with the timing of COVID-19 vaccination. • Sasaki *et al.,* 2022 (in J Diabetes Investig.): 73-year-old female who developed type 1 diabetes 28 days after dose 2 of Spikevax in Japan. She was strongly positive for autoantibodies and showed a disease-susceptible human leukocyte antigen haplotype, DRB1*04:05:01-DQB1*04:01:01... **The fourth case report was reviewed in the literature section of this current Signal Investigation. The long time to onset and apparent absence of genetic testing for this patient is noted:** • Lin *et al.,* 2023 published a case report of a 39-year-old female who developed fulminant type 1 diabetes approximately 14 weeks after a booster dose of Comirnaty. The authors reviewed other published case reports of new-onset type 1 diabetes after vaccination. They found that it tends to affect individuals aged 27–73 years, which is a later age of onset than that of non-iatrogenic type 1 diabetes. The reported symptoms include typical diabetic manifestations of polydipsia, polyuria, and polyphagia. Moreover, most of these cases (7/10) developed DKA. The symptom onset ranged from 3 days to 15 weeks after vaccination (median: 23.5 days). Moreover, most cases (9/10) in the literature were reported to occur following mRNA-based vaccination, with the exception of a case reported by Tang *et al.* in a patient who had received an inactivated virus vaccine. The HbA1c levels varied from <6.5% to 16.3% (median: 9.7%). Seven cases indicated a positive autoimmunity correlation, and five of these cases occurred in individuals with type 1 diabetes susceptibility, according to human leukocyte antigen (HLA) typing. Only one case was defined as fulminant type 1 diabetes; however, there were 2 more cases, although not stated, showing rapid onset type 1 diabetes with a lower HbA1c level. Including their patient, 4 out of 11 vaccine-related type 1 diabetes were fulminant. The authors comment that it seems that vaccine related type 1 diabetes is more likely to be fulminant. The Evaluator notes that the authors categorise their patient as having type 1B diabetes despite the patient having autoimmune antibodies detected. The long time to onset and absence of genetic testing results for this patient was also noted. **The Endocrinologist also provided a reference for a literature review of COVID-19 vaccination and new-onset autoimmune phenomena (Guo *et al.,* 2023). It proposes possible mechanisms for COVID-19 induced autoimmune disorders and includes a review of case reports, including of 13 cases of type 1 diabetes. A possible mechanism unique to Comirnaty involving MDA5 is discussed. MDA5 is a crucial innate pathogen recognition protein that has been shown to play a role in the immune response to COVID-19 mRNA vaccines. MDA5 recognizes RNA from these vaccines and triggers the synthesis of type I interferons. This immune response may interfere with insulin production, proinsulin conversion, and mitochondrial function in pancreatic β-cells, leading to the development of diabetes. They conclude that further exploration is necessary to establish a causal relationship between COVID-19 vaccines and these autoimmune diseases.**
Summary of 'signal source' section	The source of this Signal Investigation was a referral from the Pharmacovigilance Branch (PB) Principal Medical Advisor (PMA) [TRIM D23-3981730]. This vaccine-event pair was referred for a second Signal Investigation because of continued interest from a variety of stakeholders including Parliamentary Committees. s22 [redacted]. It was recommended that the Signal Investigation focus on an updated literature review and consideration of the adverse event following immunisation (AEFI) report with TGA ID #754141. This AEFI was reported to the TGA on s22 [redacted]. The Evaluator notes that 3 of the 4 case reports in the s22 [redacted] letter were reviewed in the first Signal Investigation and all 3 cases had a genetic predisposition to type 1 diabetes which was discussed by the authors. The remaining case report is reviewed in the Literature section of

	this current Signal Investigation. The long time to onset (s22) and apparent absence of genetic testing for this patient is noted s22 s22
No. of AEFI reports	**AEMS search** **a. Initial results** Date: 9 November 2023 COVID-19 Vaccine Safety Platform PTs: The following relevant PTs were selected from the Hypergylcaemia/ new onset DM standardised MedDRA query (SMQ): 1. Diabetes mellitus 2. Type 1 diabetes mellitus 3. Diabetic ketoacidosis Results: Detailed CLL TRIM D23-4059954; Comirnaty PCDs D23-4060004; Comirnaty FCDs D23-4060058.

AEFI reports by vaccine

VACCINE	NUMBER OF AEFI REPORTS
COMIRNATY	52
VAXZEVRIA	19
SPIKEVAX	7
NUVAXOVID	2
COVID-19 VACCINE TNS	1
TOTAL	81

AEFI reports by PT

PT	NUMBER OF AEFI REPORTS
DIABETES MELLITUS	32
TYPE 1 DIABETES MELLITUS	30
DIABETIC KETOACIDOSIS	26

AEFI reports by year of report

YEAR	NUMBER OF AEFI REPORTS
2021	37
2022	37
2023	7

b. Refinement of search

Two duplicates were identified (TGA ID 772053 and TGA ID 788811). The case narratives of the remaining 79 reports were reviewed to identify reports of type 2 diabetes rather than type 1. Five reports were found to be type 2 diabetes. If it was unclear whether the diagnosis was type 1 or type 2, reports were initially retained to increase the sensitivity of the search. Following removal of these reports, the number of AEFI reports associated with each vaccine is shown in the table below:

AEFI reports by vaccine with removal of type 2 diabetes reports

VACCINE	NUMBER OF AEFI REPORTS
COMIRNATY	49
VAXZEVRIA	16
SPIKEVAX	6
NUVAXOVID	2
TNS	1

TOTAL	74

The case narratives of these 74 reports were reviewed to identify reports that had a pre-existing diagnosis of diabetes. If it was unclear whether the patient had a pre-existing diagnosis of diabetes, the report was retained to increase the sensitivity of the search. Thirteen reports were found to have a previous diagnosis of diabetes. Following removal of these reports, the number of AEFI reports associated with each vaccine is shown in the table below:

AEFI reports by vaccine with removal of type 2 diabetes and pre-existing diabetes reports

VACCINE	NUMBER OF AEFI REPORTS
COMIRNATY	41
VAXZEVRIA	14
SPIKEVAX	5
NUVAXOVID	0
TNS	1
TOTAL	61

Assessment of severity

Reports with a fatal outcome

Of these 61 reports, two had a fatal outcome. As shown in the table below, neither were associated with Comirntaty.

TGA ID	AGE, GENDER, JURISDICTION	TRADE NAME OF VACCINE	PTS CODED
558227	68 F, s22	Vaxzevria	Cerebrovascular accident; Diabetic ketoacidosis; End stage renal disease; Myocardial infarction
547870	79 M, s22	Vaxzevria	Confusional state; Diabetes mellitus; Disorientation; Fall; Hypotension; Influenza like illness; Loss of consciousness

Summary of 'number of AEFI reports' section

There have been 61 reports of possible new onset type 1 diabetes to the TGA's Adverse Event Monitoring System (AEMS) in association with COVID-19 vaccines. Of these, 41 were associated with Comirnaty, 14 with Vaxzevria, 5 with Spikevax and one with a non-specified trade name. None of the reports associated with Comirnaty or Spikevax had a fatal outcome.

Report clustering and risk characterisation

As the focus of this Signal Investigation was the Comirnaty vaccine, only the 41 Comirnaty reports were characterised further. The case narratives and coding were reviewed to determine whether type 1 diabetes was specifically mentioned. Fourteen reports where type 1 diabetes was not specifically described in the coding or case narrative were excluded, leaving 27 Comirnaty reports with a higher likelihood of a type 1 diagnosis rather than a type 2 diagnosis.

Comirnaty reports by gender

As shown in the table below, the reporting rate to the TGA of type 1 diabetes associated with Comirnaty in males was higher than the reporting rate in females. This

is consistent with the epidemiology of type 1 diabetes in Australia, which has a higher incidence in males.

GENDER	REPORTS	DOSES	REPORTING RATE*
FEMALE	10	23,268,304	0.04
MALE	16	21,451,536	0.07
UNKNOWN	1	49,307	
TOTAL	27		

*Reporting rate per 100,000 doses

Comirnaty reports by age

As shown in the table below, for reports where type 1 diabetes was included in either the coding or case narrative, the 0-14 age group had the highest reporting rate, followed by the 15-24 age group and the 25+ age group had the lowest reporting rate. These results are consistent with the age specific incidence rates of type 1 diabetes in Australia.

AGE	REPORTS	DOSES	REPORTING RATES*
0-14	8	3,960,047	0.20
15-24	4	6,247,965	0.06
25+	12	34,561,124	0.03
UNKNOWN	3	11	
TOTAL	27		

*Reporting rate per 100,000 doses

Comirnaty reports by dose number

As shown in the table below, there is an apparent trend in the dose specific reporting rates, with the reporting rate of type 1 diabetes associated with Comirnaty highest with dose 1 and decreasing with subsequent doses.

DOSE	REPORTS	DOSES	REPORTING RATE*
1	10	14741229	0.07
2	6	14235231	0.04
3	5	11610948	0.04
4	1	4037722	0.02
UNKNOWN	5		
TOTAL	27		

Time to onset analysis

Of the 27 Comirnaty reports where type 1 diabetes was described in the coding or case narrative, 12 had a known time to onset (TTO). The median TTO was s22 days, the mean was s22, the modal TTO was s22 and s22 (2 reports each) and the range was s22 days. Half of the reports had a TTO of between s22 and the other half had a TTO of between s22. There is not apparent trend in the TTO of the Comirnaty reports of type 1 diabetes.

Assessment of severity

Of the 27 Comirnaty reports to the TGA in which new onset type 1 diabetes is described in the coding or case narrative, 9 (33.33%) appeared to involve an intensive care unit (ICU) admission or diabetic ketoacidosis (DKA). None had a fatal outcome. A study of newly diagnosed patients with type 1 diabetes mellitus from 2010 to 2013 in America showed that approximately 29% presented with DKA (Mencher *et al.*, 2019).

Summary of 'report clustering and risk characterisation' section	The age and gender distribution of the 27 Comirnaty reports to the TGA that describe new onset type 1 diabetes in the coding or case narrative is consistent with the background epidemiology of type 1 diabetes in Australia. The male reporting rate was higher than the female reporting rate. The 0-14 age group had the highest reporting rate, followed by the 15-24 age group. The 25+ age group had the lowest reporting rate. There is not a strong temporal relationship between Comirnaty and reports of type 1 diabetes, as there was not an apparent trend in the time to onset (TTO) of reports. There is an apparent trend in the dose specific reporting rates, with the reporting rate of type 1 diabetes associated with Comirnaty highest with dose 1 and decreasing with subsequent doses. Taken together, these findings are not supportive of a causal relationship between Comirnaty and type 1 diabetes.
Assessment of AEFI reports	The quality of the 10 most recently reported individual AEFI reports of type 1 diabetes were assessed. This includes the 7 AEFIs that been that have been reported since the completion of the first signal investigation in August 2022. Brief causality assessments were carried out in accordance with the Work Instruction '*Single AEFI Causality Assessment for Signal Investigations, version 3.0* [TRIM D23-5372930]'. The AEFI in question (type 1 diabetes) is usually idiopathic in that risk factors/ triggers/ antecedent events are often not identified. For example, although some risk factors such as family history and age are described, 85% of patients diagnosed with type 1 diabetes have no family history and it can be diagnosed at any age. Family history is more common in childhood-onset type 1 diabetes than adult-onset type 1 diabetes (Maahs *et al.*, 2010). Environmental triggers for type 1 diabetes have not been definitively identified. Diagnostic certainty was assessed as: • High if reported by a health professional or reports provided by a health professional. • Medium if reported by a consumer, JIC or sponsor but the diagnosis of type 1 diabetes is clearly described. • Low if reported by a consumer or sponsor and details insufficient to confirm that the patient was diagnosed with type 1 diabetes (e.g., diagnosis of diabetes but not type 1 diabetes was described). Of the 10 reports, diagnostic certainty was medium in 90% and high in 10%. None of the reports were provided by a health professional. Causality was un-assessable in 40% of reports, possible in 50% and unlikely in 10%. None of the 10 AEFI reports to the TGA describe the results of any genetic testing. Family history was described as being absent in 30% of reports and not described in 70% of reports. Overall, the reports have low- medium quality. Information about possible risk factors was generally lacking.

TGA ID	AGE, GENDER, JURISDICTION AND DOSE NUMBER	TIME TO ONSET AND MANAGEMENT	PTS CODED	DIAGNOSTIC CERTAINTY	CAUSALITY ASSESSMENT
726966	U age, M, s22 s22	s22	Dehydration; Eye disorder; Hypoglycaemia; Influenza like illness; Lethargy; Malaise; Myalgia; Pancreatic failure; Type 1 diabetes mellitus; Type	s22	**Possible.** s22

			2 diabetes mellitus		s22	
	730392	16 M, s22 s22	s22	Diabetes mellitus	s22	**Unlikely.** s22
	734490	20 M, s22 s22	s22		s22	**Possible.** s22

			s22		s22	
	754141	35 F, s22 s22		Chest pain; Diabetic ketoacidosis; Type 1 diabetes mellitus	s22	Possible. s22
	754788	14 M, s22 s22		Depression; Lethargy; Mood swings; Type 1 diabetes mellitus; Vomiting		Un-assessable. s22
	763233	32 F, unknown. s22		Lethargy; Palpitations; Type 1 diabetes mellitus		Un-assessable. s22
	764651	Age, gender and jurisdiction unknown. Dose number unknown		Type 1 diabetes mellitus		Un-assessable. s22
	767971	32 F, unknown jurisdiction. s22		Palpitations; Type 1 diabetes mellitus		Un-assessable. s22

		s22		s22	s22
	776016	47 M s22 s22	Diabetic ketoacidosis; Type 1 diabetes mellitus		Possible. s22
	788132	14 M, s22 s22	Abdominal pain; Asthenia; Attention deficit hyperactivity disorder; Back pain; Brain fog; Breakthrough COVID-19; Dehydration; Diarrhoea; Disability; Disturbance in attention; Fatigue; Multi-organ disorder; Musculoskeletal disorder; Neutropenia; Ocular hyperaemia; Post-acute COVID-19 syndrome; Postural orthostatic tachycardia syndrome; Type 1 diabetes mellitus; Weight decreased		Possible s22
Summary of 'assessment of AEFI reports' section	Of the 10 AEFI reports reviewed in this current Signal Investigation, diagnostic certainty was medium in 90% and high in 10%, although none of the reports had a health professional as their primary source. Causality was un-assessable in 40% of reports due to insufficient information about time to onset, possible in 50% and unlikely in 10%. None of the 10 AEFI reports to the TGA describe the results of any genetic testing. Family history was absent in 30% of reports and not described in 70% of reports. Overall, the reports have low-medium quality. Information about other possible causes/ triggers/ risk factors was generally lacking.				
Signal magnitude	**DPAR**				

There was not disproportionate reporting to the TGA of type 1 diabetes or DKA in the September-October 2023 DPAR [TRIM D23-4086242].

Reporting rate by vaccine overall

Note that the analysis below refers to the 61 reports coded with the PTs 'Type 1 diabetes mellitus', 'Diabetes mellitus' and 'Diabetic ketoacidosis' with reports of type 2 and pre-existing diabetes (according to case narrative review) removed. The AEMS search for cases to 9 November 2023 was used [TRIM D23-4059954]. The table below shows that the overall reporting rates are similar for Comirnaty, Vaxzevria and Spikevax, ranging from 0.09 to 0.10 reports per 100,000 doses).

VACCINE	TOTAL REPORTS	TOTAL DOSES*	REPORTING RATE**
COMIRNATY	41	44,769,147	0.09
VAXZEVRIA	14	13,857,711	0.10
SPIKEVAX	5	5,529,462	0.09
NUVAXOVID	0	275,865	-

*Doses to 31 October 2023 [TRIM D23-3934955]

**Reporting rate per 100,000 doses

OvE analysis

Age stratified OvE analyses were performed for type 1 diabetes and Vaxzevria and Comirnaty.

Observed cases

To increase the sensitivity of the analysis, case definitions were not applied to observed cases and all reports with the PTs 'Type 1 diabetes mellitus', 'Diabetes mellitus' and 'Diabetic ketoacidosis' were included. Reports of type 2 and pre-existing diabetes (according to case narrative review) were not removed. The AEMS search for cases to 9 November 2023 was used [TRIM D23-4059954], noting that the most recent report date was 16 October 2021.

Background rates and risk windows used

The incidence of type 1 diabetes was obtained from 2018 data from an Australian Institute of Health and Welfare (AIHW) analysis of National (insulin treated) Diabetes Register [TRIM D22-5838255 & TRIM D22-5796273]. The following age groups and rates were used in the OvE analysis:

Age group	Incidence rate per 100,000 per year
0-14 years	24
15-24 years	18
25+ years	7

A risk window of s22 days was used as all cases (with known TTO) had a TTO within this time frame, and this is a biologically plausible time frame for the development of an auto-immune condition following vaccination. Cases with unknown TTO were included in the analysis to increase the sensitivity.

Dose data

Doses administered of Comirnaty and Vaxzevria were obtained from the Australian Immunisation Register (AIR) (data processed through to 31 October 2023) [TRIM D23-4088836].

Results

The analyses are stored at TRIM D23-4088550. As shown in the tables below, the number of observed cases of type 1 diabetes for both vaccines were significantly less than the age adjusted expected number of cases. Within the individual age strata, the observed number was also significantly less than expected for both vaccines.

Comirnaty age adjusted observed versus expected analysis.

AGE GROUP	OBSERVED	EXPECTED	OVE RATIO	LL 95% CI*	UL 95% CI**
0-14 YEARS	11	109.29	0.10	0.05	0.18
15-24 YEARS	5	129.32	0.04	0.01	0.09
25+ YEARS	31	278.19	0.11	0.08	0.16
UNKNOWN	3				
TOTAL	50	516.80	0.10	0.07	0.13

*Lower limit of the 95% confidence interval
**Upper limit of the 95% confidence interval

Vaxzevria age adjusted observed versus expected analysis.

AGE GROUP	OBSERVED	EXPECTED	OVE RATIO	LL 95% CI*	UL 95% CI**
0-14 YEARS	0	0.01	0.00	#NUM!	552.34
15-24 YEARS	0	10.68	0.00	#NUM!	0.35
25+ YEARS	19	107.39	0.18	0.11	0.28
TOTAL	19	118.07	0.16	0.10	0.25

*Lower limit of the 95% confidence interval
**Upper limit of the 95% confidence interval

Summary of 'signal magnitude' section

The overall TGA reporting rates of type 1 diabetes are similar for Comirnaty, Vaxzevria and Spikevax, ranging from 0.09 to 0.10 reports per 100,000 doses. An observed versus expected (OvE) analysis using Australian background incidence rates and reports in AEMS was conducted. It was a sensitive analysis as case definitions were not applied to observed cases, all reports with the PTs 'Type 1 diabetes mellitus', 'Diabetes mellitus' and 'Diabetic ketoacidosis' were included and cases with unknown time to onset were not excluded. The number of observed cases of type 1 diabetes for both Comirnaty and Vaxzevria were significantly less than the age adjusted expected number of cases (e.g., the Comirnaty OvE ratio was 0.10 with a 95% confidence internal of 0.07-0.13). Within the individual age strata, the observed number was also significantly less than expected for both vaccines. There was not disproportionate reporting to the TGA of type 1 diabetes or DKA in association with any COVID-19 vaccines in the September-October 2023 disproportionality analysis report (DPAR). Taken together, these quantitative findings are not supportive of a causal association between Comirnaty and type 1 diabetes.

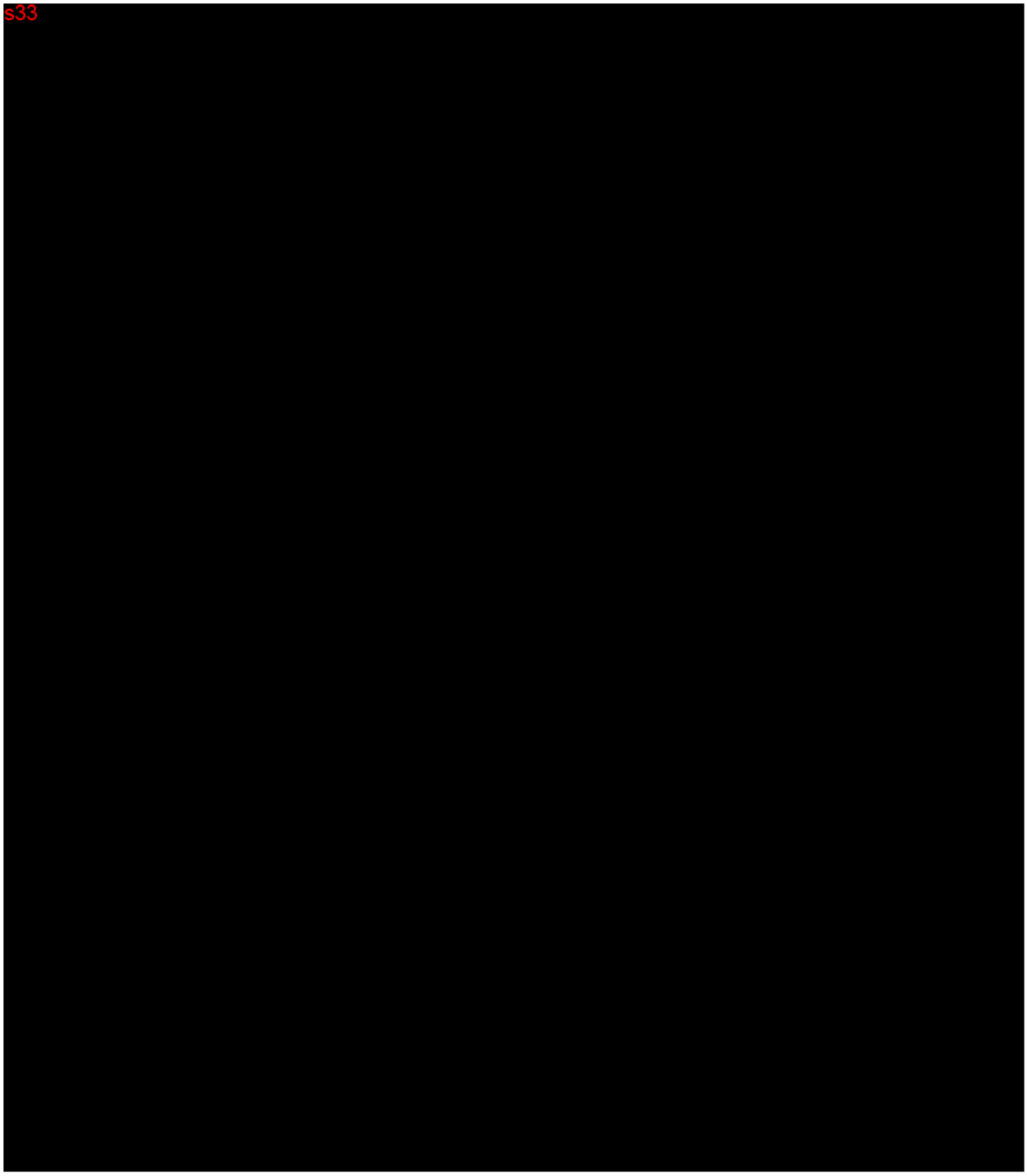
s33

[redacted]

s33

Document 2

s33



4. Literature

Literature	**Summary of literature findings from first Comirnaty and type 1 diabetes signal investigation** No formal epidemiological studies of the risk of type 1 diabetes associated with COVID-19 vaccines were located. The published literature consisted mostly of case reports of type 1 diabetes following mRNA vaccines (n=6) from Japan and Italy, with a smaller number of reports following Vaxzevria and inactivated COVID-19 vaccines. One study examined disproportionality in EudraVigilance of impaired glucose metabolism related PTs and found greater frequency with mRNA vaccines compared to adenovirus vector-based vaccines. The EudraVigilance disproportionality findings and the finding of case

reports predominantly in association with mRNA vaccines might be explained by use of mRNA vaccines in a younger age group compared to adenovirus vector-based vaccines, and the higher incidence of type 1 diabetes in younger age groups.

New PubMed search
Date: 16 November 2023
Search term: COVID-19 vaccine type 1 diabetes
Results:
This search retrieved 61 articles [TRIM D23-4143785]. The titles and abstracts of these articles were reviewed to find any studies with control groups or reviews that examined the association between COVID-19 vaccines and new onset type 1 diabetes. Case reports/ series published since the first signal investigation was completed (30 August 2022) were also selected. 12 relevant studies were found [TRIM D23-4296871].

Overall summary
Two epidemiological studies were found that examined the risk of type 1 diabetes following COVID-19 vaccination. The study by Xiong *et al.,* 2023 found no evidence of increased risks of incident diabetes following COVID-19 vaccination (Comirnaty and the inactivated SARS-CoV-2 vaccine) in a population-based cohort study. The study by Liu *et al.,* 2023 found no association between the inactivated SARS-CoV-2 vaccine and type 1 diabetes in a population-based registry. Taken together with the findings from the literature review in the first signal investigation, only one published epidemiological study with a control group was found that examined the risk of type 1 diabetes associated with Comirnaty, and this study (Xiong et al., 2023) found no evidence of increased risks of incident diabetes following Comirnaty.

Overall summary of case reports/ series:

- Preponderance of reports following mRNA vaccines but the Evaluator notes that this may represent greater use of mRNA vaccines globally, as reporting rates to TGA similar for Comirnaty and Vaxzevria.
- Majority had positive autoimmune antibodies correlation, and 50% occurred in individuals with type 1 susceptibility, according to human leukocyte antigen (HLA) typing (Lin *et al.,* 2023). Alsudais *et al.,* 2023 found a small number of new-onset diabetes cases coincidently occurring soon after the COVID-19 vaccine, especially in those with genetic susceptibility. Despite being older, these patients had a similar phenotype to type 1 diabetes.
- Of those without identified genetic susceptibility, whether genetic testing was undertaken is often not stated.
- Very wide range of time to onsets
- Most case reports/ series from Japan and Italy, similar to the literature review findings from the first Signal Investigation.

Epidemiological studies with comparison groups
Xiong *et al.,* 2023 conducted a population-based cohort study to examine the incidence of diabetes following COVID-19 vaccination (Comirnaty and the inactivated CoronaVac) and SARS-CoV-2 infection. In the first cohort (vaccinated/ unvaccinated) people who received one or more doses of COVID-19 vaccine were compared those who did not receive any COVID-19 vaccines up to September 2021. They found no evidence of increased risks of incident diabetes following CoronaVac or Comirnaty vaccination (CoronaVac: 9.08 versus 9.10 per 100,000 person-days, HR = 0.998 [95% CI 0.962 to 1.035]; Comirnaty: 7.41 versus 8.58, HR = 0.862 [0.828 to 0.897]), regardless of diabetes type. They concluded that there was no evidence of increased risks of incident diabetes following COVID-19 vaccination.

Liu *et al.,* 2023 examined the association between COVID-19 vaccination and incidence of type 1 diabetes in a population-based registry. The population only received the

inactivated SARS-CoV-2 vaccine, however. The study found that incidence was stable from 2019 to 2021, and the incidence rate did not increase when people were vaccinated in January-December 2021.

Case reports/ series and associated literature reviews

Separate to the PubMed search a conference abstract was located (Laskova et al., 2023). The abstract described a systematic review of the cases of new-onset autoimmune diabetes after the COVID-19 mRNA vaccine. Ten patients from 6 case reports and one case series were included. The authors noted that most of the patients who developed autoimmune diabetes after the COVID-19 vaccine had either personal or family history of autoimmune diseases or tested positive for certain pertinent HLA alleles.

Pezzaioli *et al.,* 2022 (Italy) conducted a literature review of endocrine adverse events associated with COVID-19 vaccines. Regarding type 1 diabetes, they found 11 case reports/case series concerning 15 patients with new onset disease following vaccination. Median age was 50 years, and eight of 15 were women. Type 1 diabetes occurred after mRNA-based vaccine in 13 of 15 cases, in one case after CoronaVac and one after Vaxzevria. Median time to onset of symptoms was 6 days, with a wide range from 3 days to 2 months. Anti-glutamic acid decarboxylase antibodies and/or insulin autoantibodies were found in nine patients. Five patients were found to have HLA haplotypes known to confer type 1 diabetes risk. They did not find any controlled studies.

Pezzaioli *et al.,* 2022 also note that the possible link between vaccinations and the occurrence of type 1 diabetes has been investigated for many different vaccines to date, such as vaccines against influenza virus A/H1N1 (131), Rotavirus, human papilloma virus (HPV), with the general agreement that vaccinations are not associated with increased risk of islet autoimmunity or type 1 diabetes. To date, only few cases of post-COVID-19 vaccination new onset diabetes have been reported, and in almost all patients a pre-existing genetic predisposition was confirmed. Therefore, these findings are too few to draw any conclusions about the possible pathogenetic mechanism.

Pezzaioli *et al.,* 2022 also found few reports of DKA in patients with pre-existing diabetes after COVID-19 vaccines (regardless of vaccine type). The available retrospective and prospective clinical studies showed that COVID-19 vaccines led to none or only temporary perturbations of blood glucose levels in patients with diabetes. Taken together, they conclude that vaccination in patients with diabetes is important because of the possible link between SARS-CoV-2 infection and islet cell degeneration and the higher risk associated with infection for patients with diabetes compared to the general population.

Alsudais *et al.,* 2023 performed a systematic review of all available case reports on the potential association between COVID-19 vaccines and type 1 diabetes. Eight eligible studies (case reports/ series) were retrieved, comprising 12 patients diagnosed with type 1 diabetes after being vaccinated with a COVID-19 vaccine. Comirnaty was given to 7 patients (58.3%), Spikevax to 2 (16.7%), the CoronaVac to one (8.3%), and Vaxzevria to one (8.3%). The last patient (8.3%) received four doses of 2 different vaccines. They first
received 2 CoronaVac doses, followed by 2 Comirnaty doses, after which symptoms appeared. Six patients (50%) reported type 1 diabetes after receiving the second dose. Five patients (41.7%) presented with diabetic ketoacidosis, of which 4 presented within the first 8 days after vaccination. Five patients (41.7%) had genetic susceptibility, with RNA binding motif protein 45 (RBM45/DRB1) and major histocompatibility complex, class II, DQ beta 1 (HLA-DQB1) mutations being prominent. The authors summarise

that they found a small number of new-onset diabetes cases coincidently occurring soon after the COVID-19 vaccine, especially in those with genetic susceptibility. Despite being older, these patients had a similar phenotype to type 1 diabetes. While there might be a causal relationship between COVID-19 vaccines and type 1 diabetes development, this should not influence decisions regarding vaccination since the overall benefit outweighs the risk. Further larger prospective trials are needed to assess causal relationship and to clarify the potential roles of COVID-19 vaccine-derived antigens in autoimmune disease development.

Lin *et al.,* 2023 (Taiwan) published a case report of a 39-year-old female who developed fulminant type 1 diabetes approximately 14 weeks after a booster dose of Comirnaty. The authors reviewed other published case reports of new-onset type 1 diabetes after vaccination. They found that it tends to affect individuals aged 27–73 years, which is a later age of onset than that of non-iatrogenic type 1 diabetes. The reported symptoms include typical diabetic manifestations of polydipsia, polyuria, and polyphagia. Moreover, most of these cases (7/10) developed DKA. The symptom onset ranged from 3 days to 15 weeks after vaccination (median: 23.5 days). Moreover, most cases (9/10) in the literature were reported to occur following mRNA-based vaccination, with the exception of a case reported by Tang *et al.* in a patient who had received an inactivated virus vaccine. The HbA1c levels varied from <6.5% to 16.3% (median: 9.7%). Seven cases indicated a positive autoimmunity correlation, and five of these cases occurred in individuals with type 1 diabetes susceptibility, according to human leukocyte antigen (HLA) typing. Only one case was defined as fulminant type 1 diabetes; however, there were 2 more cases, although not stated, showing rapid onset type 1 diabetes with a lower HbA1c level. Including their patient, 4 out of 11 vaccine-related type 1 diabetes were fulminant. It seems that vaccine related type 1 diabetes is more likely to be fulminant. The Evaluator notes that the authors categorise their patient as having type 1B diabetes despite the patient having autoimmune antibodies detected. The long time to onset and absence of genetic testing results for this patient was also noted.

Izumi et al., 2023 (Japan) published a case report of a 47-year-old male who developed fulminant type 1 diabetes several hours after receiving his third dose of Comirnaty. Through human leukocyte antigen genotyping, the disease-susceptible alleles for type 1 diabetes, DRB1*04:05 and DQB1*04:01, were identified. The patient tested positive for serum anti-glutamic acid decarboxylase (GAD) antibodies, which are normally negative for fulminant type 1 diabetes, and the authors comment that this implies that immunomodulation triggered by SARS-CoV-2 vaccination influenced the onset of type 1 diabetes. The Evaluator notes the very short time to onset. The authors speculate that although it remains unclear whether GAD antibodies were present prior to SARS-CoV-2 vaccination in their case due to the lack
of pre-treatment evaluation, it can be speculated that autoimmune processes leading to beta cell destruction had been ongoing before the vaccination, and the immune alteration caused by SARS-CoV-2 vaccination accelerated the destruction of pancreatic beta cells.

Bleve *et al.,* 2022 (Italy) published a case series of 2 patients who developed type 1 diabetes following COVID-19 vaccines. One patient developed it following Vaxzevria, and the other, a 61-year-old female developed symptoms a few days after her second dose of Comirnaty. She had a past medical history of acquired hypothyroidism. Elevated levels of anti-GAD and anti-thyroid peroxidase antibodies (Anti-TPO) were found. Genetic testing was not mentioned.

Ohuchi *et al.,* 2022 (Japan) published a case report involving a 45-year-old male who has been treated with nivolumab for advanced melanoma. One week after his final

dose of nivolumab he received a second dose of Comirnaty. Three days after the vaccination, he developed symptoms of and was diagnosed with type 1 diabetes. The diagnosis was fulminant type I diabetes mellitus caused by nivolumab, probably triggered by vaccination for COVID-19. Fulminant type 1 diabetes is one of the common immune-related adverse events (irAE) that develops in patients treated with immune checkpoint inhibitors (ICI) including nivolumab. Diabetes-related antibodies such as GAD Ab and IA-2 were negative. Genetic testing was not mentioned.

Moon *et al.,* 2023 (South Korea) published a case report involving a 56-year-old woman who developed type 1 diabetes 2 months after her second dose of Spikevax. It is reported that she had no family or personal history of type 1 diabetes or other autoimmune disorders. The patient was positive for anti-glutamic acid decarboxylase (GAD) antibody. Genetic testing was not mentioned.

Aydogan *et al.,* 2022 (Turkey) present a case series of 4 patients diagnosed with type 1 diabetes following Comirnaty. All were positive for GAD autoantibodies, but none appear to have been tested for genetic susceptibility:

- 56-year-old male, with a history of autoimmune disorders, namely vitiligo and Hashimoto's thyroiditis. 15 days after his second dose of Comirnaty he developed symptoms of type 1 diabetes.
- 48-year-old male with no personal or family history of autoimmunity or diabetes mellitus. Two months after his second dose of Comirnaty he developed symptoms of type 1 diabetes.
- 27-year-old female with no personal or family history of autoimmune disorders who developed symptoms about 3 weeks after her second dose of Comirnaty.
- 36-year-old male with no personal or family history of autoimmunity or diabetes mellitus who developed symptoms of type 1 diabetes about 3 weeks after his second dose of Comirnaty.

Kobayashi *et al.,* 2022 present a case report of a 59-year-old male with no family history of diabetes or autoimmune diseases who developed symptoms of type 1 diabetes 15 weeks after his second dose of Comirnaty. He was diagnosed with upper respiratory inflammation and was prescribed antibiotics and antipyretics following vaccination and before the onset of type 1 diabetes symptoms. He was found to be positive for GAD autoantibodies. HLA analysis showed genotypes with susceptibility to fulminant type 1 diabetes (DRB1*04:05:01/09:01:02- DQB1*03:03:02/04:01:01).

Huang et al., 2023 present a case of a 39 year old female who developed type 1 diabetes 4 days after her fourth dose of SARS-CoV-2 protein subunit vaccination (Zifivax). It is reported that she had a family history of diabetes but the type is not specified. She was negative for GAD autoantibodies.

Literature regarding the mechanism

Vaccination induced type 1 diabetes is hypothesized to be caused by molecular mimicry-related cross-reactivity between SARS-CoV-2 antigens and receptors involved in autoimmunity or autoimmune/inflammatory syndrome induced by adjuvants (ASIA). Molecular mimicry of SARS-CoV-2 peptides in both the vaccine and human tissue antigens, may cross-react and possibly result in autoimmunity. It is possible that the spike protein in the SARS-CoV-2 vaccines could cross-react with the ACE2 receptors of islet cells target proteins due to molecular mimicry to cause islet cells damage. The presence of ASIA is another possible contributory factor, as adjuvants serve as immunological or pharmacological agents, thus enhancing the effectiveness of the vaccine by interfering with innate immunity and subsequently causing autoimmune disease in genetically susceptible individuals (Lin *et al.,* 2023).

Comirnaty does not contain classical adjuvants. Instead, self-adjuvant features of "mRNA", and polyethylene glycol lipid conjugates that act as adjuvants in mRNA-based SARS-CoV-2 vaccines have been suggested to trigger autoimmune reactions (Aydogan *et al.,* 2023). Another mechanism may be an exacerbation caused by the immune-stimulating effects of vaccines in individuals with an individual predisposition to autoimmunity.

Sasaki *et al*., 2022 proposed that there might not be a single mechanism responsible for the loss of islet function and the development of hyperglycemia associated with Covid-19 vaccination, as new-onset type 1 diabetes patients with positive autoantibodies developed symptoms 4-7 weeks after vaccination, while patients with negative autoantibodies showed symptoms within a week after vaccination.

Guo *et al*., 2023 published a literature review of COVID-19 vaccination and new-onset autoimmune phenomena. They propose possible mechanisms for COVID-19 induced autoimmune disorders and include a review of case reports, including of 13 cases of type 1 diabetes. A possible mechanism unique to mRNA vaccines involving MDA5 is discussed. MDA5 is a crucial innate pathogen recognition protein that has been shown to play a role in the immune response to COVID-19 mRNA vaccines. MDA5 recognizes RNA from these vaccines and triggers the synthesis of type I interferons. This immune response may interfere with insulin production, proinsulin conversion, and mitochondrial function in pancreatic β-cells, leading to the development of diabetes.

Guo *et al.,* 2023 conclude that rare autoimmune diseases may potentially arise following COVID-19 vaccination, such as autoimmune glomerulonephritis, autoimmune rheumatic diseases, and autoimmune hepatitis, among others. They outline that the true incidence of these diseases after vaccination remains difficult to determine however, as not all cases are or will be reported. Thus, further exploration is necessary to establish a causal relationship between COVID-19 vaccines and the aforementioned autoimmune diseases.

SARS-CoV-2 infection and type 1 diabetes

Bombaci *et al.,* 2023 examined the epidemiological trend of type 1 diabetes during the pandemic, the diabetogenic role of SARS-CoV-2, and the influence of pre-existing type 1 diabetes on COVID-19 outcomes. They conclude that the incidence of type 1 diabetes has considerably changed during the COVID-19 pandemic, but any direct role of SARS-CoV-2 is uncertain. It is more likely that SARS-CoV-2 infection acts as an accelerator of pancreatic β-cell immunological destruction, which is activated by known viral triggers whose spread has been abnormal during these pandemic years. Tiberti *et al.,* 2023 also did not confirm a role for COVID-19 as a potential trigger of type 1 diabetes autoimmunity and did not find evidence of an increased frequency of SARS-CoV-2 antibodies in newly diagnosed type 1 diabetes patients in comparison with healthy population.

Regarding mRNA vaccines for COVID-19, Bombaci *et al.,* 2023 note that the safety of vaccination against SARS-CoV-2 in people with diabetes has been demonstrated by the absence of relevant alterations in glucose control within the following days. It has been demonstrated that paediatric patients with type 1 diabetes and COVID-19 are at higher risk of hospitalization than a healthy age-matched population due to several reasons, mainly to due to the occurrence of metabolic decompensation and DKA. Therefore, they are supportive of vaccination of children and adolescents with type 1 diabetes.

Literature regarding other vaccines and type 1 diabetes

	As childhood immunization programs have expanded, there has been speculation that vaccines may play a role in the development of childhood diseases that have risen in incidence, such as type 1 diabetes (Rewers *et al.,* 2015). However, no association between immunizations and islet autoimmunity or type 1 diabetes has been found thus far. A meta-analysis reviewed 23 studies investigating 16 vaccinations and analyzed 11 studies that met the inclusion criteria (Morgan *et al.,* 2016). Overall, there was no evidence to suggest an association between any of the childhood vaccinations investigated and type 1 diabetes. The pooled odds ratios ranged from 0.58 (95% CI 0.24–1.40) for the measles, mumps, and rubella (MMR) vaccination in five studies up to 1.04 (95% CI 0.94–1.14) for the haemophilus influenza B (HiB) vaccination in 11 studies. Significant heterogeneity was present in most of the pooled analyses but was markedly reduced when analyses were restricted to study reports with high methodology quality scores.
Summary of 'literature' section	Taken together with the findings from the literature review in the first signal investigation, only one published epidemiological study with a control group was found that examined the risk of type 1 diabetes associated with Comirnaty, and this study (Xiong et al., 2023) found no evidence of increased risks of incident diabetes following Comirnaty. In the published case reports and series, there is a preponderance of reports following mRNA vaccines but the Evaluator notes that this may represent greater use of mRNA vaccines globally, as reporting rates of type 1 diabetes to the TGA are similar for Comirnaty and Vaxzevria. In addition, approximately 50% occurred in individuals with type 1 susceptibility, according to human leukocyte antigen (HLA) typing (Lin et al., 2023). The Evaluator notes that of those without identified genetic susceptibility, whether genetic testing was undertaken is often not stated. The case reports and series have a very wide range of time to onsets. Similar to the findings from the first Signal Investigation, most of the case reports/ series are from Italy and Japan. Alsudais et al., 2023 found a small number of new-onset diabetes cases coincidently occurring soon after the COVID-19 vaccine, especially in those with genetic susceptibility. Despite being older, these patients had a similar phenotype to traditional type 1 diabetes. Overall, the literature findings are not supportive of a causal association between Comirnaty and type 1 diabetes.
Biological plausibility	No association between non-COVID-19 immunisations and islet autoimmunity or type 1 diabetes has been found thus far. A meta-analysis reviewed 23 studies investigating 16 vaccinations and analysed 11 studies that met the inclusion criteria (Morgan et al., 2016). Overall, there was no evidence to suggest an association between any of the childhood vaccinations investigated and type 1 diabetes. Mechanisms for COVID-19 vaccines to cause type 1 diabetes have been proposed such as molecular mimicry-related cross-reactivity between SARS-CoV-2 antigens and receptors involved in autoimmunity or autoimmune/inflammatory syndrome induced by adjuvants (Lin et al., 2023). A specific mechanism for mRNA vaccines has been proposed, involving a protein called MDA5 (Guo et al., 2023). These mechanisms have not been proven however, and Guo et al., 2023 conclude that further exploration is necessary to establish a causal relationship between COVID-19 vaccines and autoimmune diseases such as type 1 diabetes.

5. Regulatory surveillance

Australian regulatory surveillance	**Product Information (PI)** Diabetes is not listed as an adverse event in the following product information documents: • Comirnaty PI, last updated 6 September 2023, TRIM D23-4357255 • Spikevax PI, last updated 24 April 2023, TRIM D23-4357384 • Nuvaxovid PI, last updated 26 October 2023, TRIM D23-4357435 • Vaxzevria PI, last updated 17 April 2023, TRIM D23-4357483. **Applicable clinical guidance**

	Information about COVID-19 vaccines from the Australian Immunisation Handbook (last updated 27 November 2023, TRIM D23-4351792) The Australian Technical Advisory Group on Immunisation recommends further doses of COVID-19 vaccine for people with diabetes mellitus requiring medication because of their increased risk of severe COVID-19. Diabetes is not described as an adverse effect associated with any COVID-19 vaccine.
	Sponsor's PSUR/MSSR/SSR
	Comirnaty Periodic Safety Update Report #5 covering the period 19 December 2022 to 18 June 2023 [TRIM D23-3125594] The TGA's Risk Management Section (RMS) conducted a review of the 6 month Periodic Safety Update Report (PSUR) for Comirnaty (Comirnaty Original, Comirnaty bivalent Original/ Omicron BA.1, Comirnaty bivalent Original/ Omicron BA.4-5), covering period 19 December 2022 through 18 June 2023: D23-3277505. Diabetes was not identified as a safety concern. Appendix 5.8 of the Sponsor's PSUR contains OvE analyses for adverse events of special interest. Type 1 diabetes is considered an AESI. In overall and age stratified OvE analyses, the observed number of reports of type 1 diabetes in association with Comirnaty globally is less than expected based on the background incidence of type 1 diabetes.
Summary of 'Australian regulatory surveillance' section	Type 1 diabetes is not listed as an adverse event in the Australian Product Information documents for any COVID-19 vaccines, nor in the Australian Immunisation Handbook. Patients with diabetes requiring insulin treatment are identified by the Australian Technical Advisory Group as being at increased risk of severe COVID-19 infection. The TGA's Risk Management Section (RMS) conducted a review of the Sponsor's 6-month Periodic Safety Update Report (PSUR) for Comirnaty, covering the period 19 December 2022 through 18 June 2023: D23-3277505. Diabetes was not identified as a safety concern. Appendix 5.8 of the Sponsor's PSUR contains OvE analyses for adverse events of special interest. Type 1 diabetes is considered an AESI. In overall and age stratified OvE analyses, the observed number of reports of type 1 diabetes in association with Comirnaty globally is less than expected based on the background incidence of type 1 diabetes.
US FDA	**Label**
	Diabetes is not listed as an adverse event in the FDA Comirnaty label (last updated 31 October 2023).
	Relevant regulatory action
	Diabetes is not discussed as a COVID-19 vaccine safety issue at the following meetings of the Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER) Vaccines and Related Biological Products Advisory Committee (VRBPAC) Meetings: • 5 October 2023 (https://www.fda.gov/media/173168/download) • 15 June 2023 (https://www.fda.gov/media/169804/download) • 26 January 2023 (https://www.fda.gov/media/165307/download) The Advisory Committee on Immunisation Practices (ACIP) CDC has not discussed diabetes as a vaccine safety issue: www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/covid-19.html
EU EMA	**Summary of Product Characteristics (SmPC)**

	Diabetes is not listed in as adverse event in the EMA Comirnaty SmPC (last updated 31 October 2023). **Relevant regulatory action** Diabetes was not identified as a safety concern in relation to COVID-19 vaccines in the following EMA Pharmacovigilance Risk Assessment Committee (PRAC) meeting minutes: • 25-28 September 2023 • 28-31 August 2023 • 3-6 July 2023 [TRIM D23-4387176]. In the 3-6 July 2023 minutes, the following information about Spikevax is included: *In addition, PRAC recommended an update of the list of safety concerns in the RMP by removing the following safety concerns: vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) as important potential risk and use in immunocompromised subjects, interaction with other vaccines, use in frail subjects with unstable health conditions and co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) and use in subjects with autoimmune or inflammatory disorders as missing information'.* The Evaluator interprets this as meaning that use in frail subjects with conditions such as diabetes is no longer considered 'missing information'.
UK MHRA	**Summary of Product Characteristics (SPC)** Diabetes is not listed in as adverse event in the MHRA Comirnaty SmPC (last updated 4 September 2023). **Relevant regulatory action** The final 'MHRA Coronavirus vaccine –summary of Yellow Card reporting', updated on 8 March 2023 does not identify diabetes as a safety concern.
Health Canada	**Product Monograph** Diabetes is not listed in as adverse event in the Health Canada Comirnaty PM (last updated 28 September 2023). **Relevant regulatory action** The Health Canada 'Reported side effects following COVID-19 vaccination in Canada' (last updated 29 September 2023) does not identify diabetes as a safety concern.
NZ Medsafe	**Datasheet** Diabetes is not listed in as adverse event in the Health Canada Comirnaty PM (last updated 15 November 2023). **Relevant regulatory action** Medsafe's final 'Adverse events following immunisation with COVID-19 vaccines: Safety Report #46' (30 November 2022) does not identify diabetes as a safety concern.
Other international regulators	Type 1 diabetes and COVID-19 vaccines has not been a topic discussed in previous International Post Market Surveillance Teleconferences (IPMST) [TRIM D18-10994661].

Summary of 'international regulatory surveillance' section	No other regulator is investigating the signal of Comirnaty and type 1 diabetes or have updated their product information documents to include it as an adverse event.

6. Impact

Impact on clinical practice	Diabetic ketoacidosis (DKA) is a serious, potentially lethal complication of type 1 diabetes mellitus that may be present at diagnosis. A study of newly diagnosed patients with type 1 diabetes mellitus from 2010 to 2013 in America showed that approximately 29% presented with DKA (Mencher *et al.*, 2019). Consistent with this study, of the 27 Comirnaty reports to the TGA in which new onset type 1 diabetes is described in the coding or case narrative, 9 (33.33%) appeared to involve an intensive care unit (ICU) admission or diabetic ketoacidosis. None had a fatal outcome. Both type 1 and type 2 diabetes are associated with long-term complications such as blindness, amputations, heart disease and kidney disease. If complications develop, diabetes can have a significant impact on quality of life and can reduce life expectancy. Patients with diabetes are at a high risk of adverse outcomes after COVID-19 infection, and infection itself can be associated with severe hyperglycaemia, including hyperglycaemic emergencies. The safety of vaccination against SARS-CoV-2 in people with diabetes has been demonstrated by the absence of relevant alterations in glucose control within the following days. It has been demonstrated that paediatric patients with type 1 diabetes and COVID-19 are at higher risk of hospitalization than a healthy age-matched population due to several reasons, mainly to the occurrence of metabolic decompensation and DKA (Bombaci *et al.*, 2023). Accordingly, ATAGI has identified patients with diabetes as a priority group for COVID-19 vaccination.
Summary of 'impact on clinical practice' section	The severity of type 1 diabetes is acknowledged, especially diabetic ketoacidosis (DKA), which is a frequent presentation. However, given the current lack of evidence linking Comirnaty with the development of type 1 diabetes, the higher risk of SARS-CoV-2 infection in patients with type 1 diabetes, the demonstrated safety of vaccination in patients with diabetes, presently there is no overall benefit in alerting clinicians to a possible link between Comirnaty and type 1 diabetes through regulatory action.

s22 [redacted]

s22 [redacted]

Impact on other priority populations	N/A

s22 [redacted]

7. Conclusion

Concluding statement, recommendations and rationale	See below
Summary of 'concluding statement, recommendations and rationale' section	Currently, there is insufficient evidence of a causal relationship between Comirnaty and new onset type 1 diabetes. Like the Sponsor's global OvE analyses, conservative age adjusted OvE analyses using Australian background incidence rates and reports in AEMS showed significantly less cases of type 1 diabetes than expected for Comirnaty. The overall TGA reporting rates of type 1 diabetes are similar for Comirnaty, Vaxzevria and Spikevax. Only one published epidemiological study with a control group was found that examined the risk of type 1 diabetes associated with Comirnaty, and this study (Xiong et al., 2023) found no evidence of increased risks of incident diabetes following Comirnaty. No other regulator is investigating the signal or have updated their PIs. Overall, of the sample examined, the reports of type 1 diabetes to the TGA in association with Comirnaty are low- medium quality and information about other possible risk factors is generally lacking. Their age and gender distribution (higher reporting rate in males and younger age groups) are consistent with the background epidemiology of type 1 diabetes and no trend in TTO was identified. s33 [redacted] s33 [redacted] s33 [redacted] Taken together with the greater use of Comirnaty (compared to other COVID-19 vaccines) in children, these results do not substantiate evidence of a causal association between Comirnaty and type 1 diabetes. There was not disproportionate reporting to the TGA of type 1 diabetes or DKA in association with any COVID-19 vaccines in the recent DPAR report. Given the current lack of evidence linking Comirnaty with the development of type 1 diabetes, the higher risk of SARS-CoV-2 infection in patients with type 1 diabetes, the demonstrated safety of vaccination in patients with diabetes, presently there is no overall benefit in alerting clinicians to a possible link between Comirnaty and type 1 diabetes through

<table>
<tr><td></td><td colspan="2">regulatory action. This signal can be returned to routine pharmacovigilance monitoring.</td></tr>
<tr><td>Proposed action</td><td colspan="2">☐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</td></tr>
<tr><td>Instructions for Stream B, MAVIS Evaluation Stream (if applicable)</td><td colspan="2">• N/A</td></tr>
<tr><td rowspan="11">Instructions for Stream C, ROS (if applicable)</td><td colspan="2">Proposed regulatory action</td></tr>
<tr><td>☐PI/CMI update</td><td>☐Recall</td></tr>
<tr><td>☐Safety alert</td><td>☐IPMST topic</td></tr>
<tr><td>☐Medicines Safety Update (MSU)</td><td>☐Pregnancy Category update</td></tr>
<tr><td>☐DHCP Letter</td><td>☐External/Internal liaison (specify)</td></tr>
<tr><td>☐RMP update</td><td>☐Other (specify)</td></tr>
<tr><td colspan="2">Statement on validity/public health impact</td></tr>
<tr><td colspan="2">N/A</td></tr>
<tr><td colspan="2">Specific instructions for selected regulatory action(s)</td></tr>
<tr><td colspan="2">N/A</td></tr>
<tr><td>Instructions for <Other> (if applicable)</td><td colspan="2">N/A</td></tr>
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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:
D21-3334656

Vaxzevria ChAdOx1-S (previously COVID-19 Vaccine AstraZeneca) and Comirnaty (BNT162b2 [mRNA]) COVID-19 vaccine and Cerebrovascular Accident (CVA)/Stroke

Date and Time completed	30/11/2021 5:00 PM

Summary

The issue of Vaxzevria ChAdOx1-2 (previously COVID-19 Vaccine AstraZeneca) and risk of cerebrovascular accident (CVA)/stroke was referred for a Targeted Investigation Process (TIP) review following a potential signal identified in the TGA's routine disproportionality analysis (DPAR; using adverse event reporting data from March-June 2021). Review of an article published in the British Medical Journal (BMJ; Hippisley-Cox et al. 2021 D21-3335135) resulted in the addition of Comirnaty (BNT162b2 [mRNA]) COVID-19 vaccine to this TIP.

A stroke or 'cerebrovascular accident' (CVA) refers to damage to the brain because of an interruption to its blood supply. It is a medical emergency that requires prompt treatment as death of brain cells occurs within minutes and may lead to significant disability or death. There are two broad types of stroke, ischaemic and haemorrhagic. Ischaemic strokes are associated with narrowing or blockage of blood vessels and account for 80% of all strokes. Haemorrhagic strokes are associated with blood vessels that have leaked or ruptured and account for 20% of strokes. Risk factors for stroke include age (>55 years), race (African American and Asian individuals have a higher risk), gender (male), high blood pressure, cigarette smoking, high cholesterol, diabetes, obstructive sleep apnoea, cardiovascular disease (including heart failure and abnormal heart rhythms such as atrial fibrillation), cocaine use, and personal or family history of stroke/transient ischaemic attack/heart attack.

Stroke/CVA falls under the 'Coagulation disorder' TGA Adverse Event of Special Interest (AESI) related to COVID-19 disease (Category 3 AESI). There is currently no Brighton Collaboration Case Definition for stroke/CVA.

A review of reports to the TGA's Adverse Event Management System (AEMS) database on 22 November 2021 identified a total of 612 ischaemic central nervous system vascular conditions, of which 461 were associated with Vaxzevria, 145 with Comirnaty, 5 with COVID-19 vaccine trade name not specified, and 3 with Spikevax (Moderna – elasomeran). Four hundred and sixty four (464) haemorrhagic central nervous system vascular conditions were also identified, of which 351 were associated with Vaxzevria, 106 with Comirnaty, and 5 with Spikevax. These reports were identified using standardised medDRA queries (SMQ) searches on Qlik which included a wide range of ischaemic and haemorrhagic stroke preferred terms (PT's). Note was made that there was some overlap in the PT's included in these searches, with some cases identified in both ischaemic and haemorrhagic central nervous system vascular condition SMQ searches. Specifically, 349 cerebrovascular accidents, 4 cerebellar stroke, 2 brain stem stroke, 1 basal ganglia stroke, 1 cerebrovascular disorder, and 1 vertebrobasilar stroke were identified in both ischaemic and haemorrhagic SMQ searches.

The ischaemic and haemorrhagic cases associated with Vaxzevria were reported more in males, older individuals (75 years and over), and following dose 1. Forty two (42) ischaemic reports were fatal, and 65 haemorrhagic reports were fatal. Notably only 1 fatal case was reported to reside in aged/residential care. In

relation to thrombosis with thrombocytopenia syndrome (TTS), 16 reports were confirmed cases of TTS, 4 were probable cases of TTS, and 6 cases were under investigation for possible TTS.

The ischaemic and haemorrhagic cases associated with Comirnaty were reported more in females, middle-aged individuals (45-64 years), and following dose 1. Twenty five (25) ischaemic reports were fatal, and 24 haemorrhagic reports were fatal. Nineteen (19) of these fatal cases resided in aged/residential care.

A total of 2 ischaemic and 5 haemorrhagic reports to AEMS were associated with Spikevax. The majority of these reports were in females.

An observed versus expected (O/E) analysis was requested from the Vaccine Epidemiology Response and Action (VERA) team for this signal in order to determine if the number of reports received is above expected, however the analysis was not yet available at the time of this TIP review. Similarly, reporting rates were not able to be calculated without the O/E results, as the observed number from the O/E analysis would be used in this calculation (that is, number of reports excluding reports of TTS or Cerebral Venous Sinus Thrombosis).

The sponsor's Monthly Safety Summary Report (MSSR) (1 August -30 September 2021) for Vaxzevria reported no signal for the AESI term 'embolic and thrombotic events (thrombosis)' which included haemorrhagic and ischaemic stroke. However, this AESI term was noted to include a wide range of non-stroke terminology such as mesenteric arteriosclerosis, pulmonary artery occlusion, iliac vein occlusion, and disseminated intravascular coagulation. The Vaxzevria MSSR therefore did not include a specific observed versus expected (O/E) analysis or discussion regarding the risk of stroke (ischaemic or haemorrhagic) following Vaxzevria administration.

The sponsor's Monthly Safety Summary Report (MSSR) (1 October - 31 October 2021) for Comirnaty reported no signal for ischaemic or haemorrhagic stroke. Separate O/E analysis for ischaemic and haemorrhagic strokes reported fewer reports of observed than expected cases overall and in age stratified analyses.

s33 [redacted]

Studies utilising self-controlled case series methodology and national data from the United Kingdom describe increased rates of arterial thromboembolism, ischaemic stroke, and haemorrhagic stroke following Comirnaty compared to background rates. Published case reports also discuss ischaemic and haemorrhagic strokes following Vaxzevria and suggest that these conditions may sit on the spectrum of TTS/vaccine induced immune thrombotic thrombocytopenia (VITT), with both haemorrhagic and ischaemic cases occurring without thrombocytopenia.

s33 [redacted]

Stroke/CVA is not included in the Australian or International Product Information (PI's) for Vaxzevria or Comirnaty. Notably, the European Medicines Agency (EMA) Summary of Product Characteristics (SmPC) was updated on 24 November 2021 to include information regarding events of cerebrovascular venous and sinus thrombosis without thrombocytopenia (under Section 4.4 Special warnings and precautions for use). This information is not included in the current Australian PI for Vaxzevria.

s33 [redacted]

Recommendations

Request the Australian sponsors for Comirnaty and Vaxzevria to provide a review of ischaemic and haemorrhagic stroke, including an observed versus expected analysis. This analysis should include a discussion regarding the preferred terms (PT's) included and excluded, the background rates utilised, and an age and gender stratified analysis.

Commented s22 Note that an O/E analysis from VERA is pending and has not been included in this report.

Commente s22 Thank you. Noted.

The analysis provided by the Australian sponsors for Comirnaty and Vaxzevria should be sent to Evaluation stream for review. The review should also take into consideration the Australian reporting rates and observed versus expected numbers of ischaemic and haemorrhagic stroke reports, provided by VERA. The purpose of this review would be to determine the appropriateness of current risk minimisation activities (e.g. whether a PI update is required).

Consider the PT's included in the current AESI list for Stroke (as of 30 November 2021 stroke falls within a new category of 'CNS haemorrhages and cerebrovascular accidents', see D21-3378171). The following PT's are mapped to this AESI: basal ganglia stroke, brain stem stroke, cerebellar stroke, embolic stroke, lacunar stroke, spinal stroke, thrombotic stroke, vertebrobasilar stroke, cerebral infarction, cerebrovascular accident, ischaemic stroke, ischaemic cerebral infarction, transient ischaemic attack, haemorrhagic cerebral infarction, haemorrhagic stroke, haemorrhagic transformation stroke, and cerebral small vessel ischaemic disease. It is suggested that additional PT's could be added to this mapping, specifically: Brain stem haemorrhage, Cerebral haematoma, Cerebral haemorrhage, Haemorrhage intracranial, Intracranial haematoma, Subarachnoid haemorrhage, Basal ganglia infarction, Basilar artery thrombosis, Cerebral thrombosis, Lacunar infarction, Pituitary infarction, Retinal artery occlusion, Cerebral artery thrombosis, Thalamic infarction, Amaurosis fugax, Carotid artery thrombosis, Cerebellar infarction, Cerebral ischemia, Basilar artery occlusion, Cerebellar artery thrombosis, Cerebral artery stenosis, and Cerebrovascular disorder. In addition, the AESI could be separated out to haemorrhagic and ischaemic stroke AESI terms to assist analysis.

Priority

High

MO5/Stream lead Advice

This TIP was discussed at the MAVIS issues meeting on Monday 13 December 2021. The MAVIS MO5 and Evaluation Stream lead agreed with the recommendations proposed above. A representative from VERA acknowledged that VERA's involvement in the O/E analysis for CVA/stroke would be followed up after the meeting.

Based on current procedures, the Vaccine-STRS stream lead confirmed with the Regulatory Outcomes stream (ROS) lead that ROS would send the above request for information to the sponsors for Comirnaty and Vaxzevria.

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

s33

2. Vaccine information

Indication(s)	Vaxzevria ChAdOx 1-S received provisional approval for active immunisation of individual ≥ 18 years old for the prevention of COVID-19 caused by SARS-CoV-2 on 15 February 2021. See Vaxzevria PI D21-3383610. Comirnaty (BNT162b2 [mRNA]) COVID-19 Vaccine Pfizer received provisional approval for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older on 25 January 2021 (for 16 years and over), 22 July 2021 (for 12 years and over), and 26 October 2021 (booster dose for 18 years and over). See Comirnaty PI D21-3383601.
Vaccine roll-out status	In relation to Vaxzevria, the following recommendations have been made by the ATAGI (see ATAGI clinical guidance version 7.4, last updated 29 October 2021 at D21-3383662): • mRNA vaccines (i.e., Comirnaty or Spikevax) are preferred over Vaxzevria in people aged <60 years, and in pregnant people. Vaxzevria continues to be recommended in people aged 18 to <60 years when the benefits outweigh risks, including in outbreak settings. • Severely immunocompromised individuals are recommended to receive a third dose of a COVID-19 vaccine, 2-6 months after their second dose. An mRNA COVID-19 vaccine (i.e., Comirnaty or Spikevax) is preferred for this third dose, but Vaxzevria is also acceptable in certain circumstances. • Vaxzevria is associated with a rare risk of thrombosis with thrombocytopenia syndrome (TTS). The risk of TTS is higher in younger

adults than in older adults and is higher after the first dose than the second. Comirnaty and Spikevax are not associated with a risk of TTS.

- Contraindications to Vaxzevria include anaphylaxis to a previous dose or to an ingredient; history of capillary leak syndrome; and, thrombosis with thrombocytopenia after a previous dose, or any other serious adverse event attributed to a previous dose.

In relation to Comirnaty, the following recommendations have been made by the ATAGI (see ATAGI clinical guidance version 7.4, last updated 29 October 2021 at D21-3383662):

- mRNA vaccines (i.e. Comirnaty or Spikevax) are the preferred vaccines in people aged <60 years and in pregnant women
- Comirnaty is recommended as a single booster dose for people who completed their primary COVID-19 vaccine course >6months ago. Comirnaty is the preferred brand for booster doses, regardless of the brand used in the primary course.
- Severely immunocompromised individuals are recommended to receive a third dose of a COVID-19 vaccine, 2-6 months after their second dose. An mRNA COVID-19 vaccine (i.e. Comirnaty or Spikevax) is preferred for this third dose, but Vaxzevria is also acceptable in certain circumstances.
- Either Comirnaty or Spikevax is recommended in people with a past history of certain precautionary conditions for Vaxzevria; cerebral venous sinus thrombosis (CVST), heparin induced thrombocytopaenia (HIT), idiopathic splanchnic (mesenteric, portal, splenic) vein thrombosis, and antiphospholipid syndrome with thrombosis. Comirnaty or Spikevax are recommended for the second dose for people in these groups who have received a first dose of COVID-19 Vaccine AstraZeneca.
- Contraindications to Comirnaty include anaphylaxis to a previous dose or to an ingredient of an mRNA COVID-19 vaccine, or any other serious adverse event attributed to a previous dose
- Precautionary conditions specific to Comirnaty and Spikevax include recent (i.e. within the last 3 months) myocarditis or pericarditis; acute rheumatic fever or acute rheumatic heart disease (wit evidence of active inflammation); or acute decompensated heart failure. People with these conditions can still receive Comirnaty or Spikevax; however consultation with a GP, immunisation specialist or cardiologist is recommended prior to vaccination to discuss the best timing of vaccination and to consider if any additional precautions are needed.

ATAGI also recommends the following

- COVID-19 vaccines can be co-administered (i.e. on the same day) with an influenza vaccine and with other vaccines, if required. However, given the limited evidence in this space, providers need to balance the opportunistic need for co-administration with giving the vaccines on separate visits. There is a potential for an increase in mild to moderate adverse events when more than one vaccine is given at the same time.
- Recording of COVID-19 vaccine administration in the Australian Immunisation Register (AIR) is mandatory.
- Notification of adverse events following immunisation should be made through the specified reporting mechanisms for your state or territory, or to the Therapeutic Goods Association (TGA)

	• People who have received an anti-SARS-coV-2 monoclonal antibody or convalescent plasma should defer future doses of COVID-19 vaccine for at least 90 days.
Mechanism of action	Vaxzevria 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. See Vaxzevria PI D21-3383610. Comirnaty 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. See Comirnaty PI D21-3383601.

3. Adverse event information

Signal Source	The source of this signal was the March-June vaccine DPAR (see D21-3124789) which flagged Vaxzevria and the following PT's: cerebral haemorrhage, cerebral infarction, cerebrovascular accident, haemorrhage intracranial, subarachnoid haemorrhage, ischaemic stroke, and transient ischaemic attack. Given the overlapping nature of these terms and that 'stroke' falls within an AESI category for COVID-19 disease, the DPAR evaluator decided to group these terms together within the one targeted investigation for 'cerebrovascular accident'. No 'cerebrovascular accident' related terms flagged on the March-June DPAR for Comirnaty. An article published in the BMJ (see D21-3335135 and the Literature review section of this report) was identified on 2 September 2021 which resulted in the addition of Comirnaty to this TIP topic (see email at D21-3335495).
AESI status	'Cerebrovascular stroke' falls under 'Coagulation disorder' which is a Category 3 AESI – related to COVID-19 disease (see D20-3595626). The following stroke related PT's are mapped to this AESI: General stroke PTs: • Basal ganglia stroke • Brain stem stroke • Cerebellar stroke • Embolic stroke • Lacunar stroke • Spinal stroke • Thrombotic stroke • Vertebrobasilar stroke • Cerebral infarction • Cerebrovascular accident Ischaemic stroke PTs: • Ischaemic stroke • Cerebral small vessel ischaemic disease • Ischaemic cerebral infarction

	• Transient ischaemic attack Haemorrhagic stroke PTs: • Haemorrhagic cerebral infarction • Haemorrhagic stroke • Haemorrhagic transformation stroke 'Stroke' or cerebrovascular accident does not have a Brighton Collaboration criteria.
AEFI	A stroke or 'Cerebrovascular accident' refers to damage to the brain as a result of interruption to its blood supply. It is a medical emergency that requires prompt treatment, as death of brain cells occurs within minutes and may lead to significant disability or death. There are two broad types of stroke, both of which result in reduced blood supply to the brain: - Ischaemic: Associated with narrowing or blockage of blood vessels. This is the most common form of stroke, accounting for 80% of all strokes. Ischaemic strokes may be due to thrombosis (a local in situ obstruction e.g. atherosclerosis, giant cell arteritis, fibromuscular dysplasia), embolism (particles that have originated elsewhere and blocked an artery e.g. cardiac emboli), or due to systemic hypoperfusion. o A transient ischaemic attack (TIA) is a specific subtype of ischaemic stroke. It is warning or 'mini-stroke' that is characterised by a temporary period (<24hours) of stroke-like symptoms due to a transient period of brain ischemia. - Haemorrhagic: Associated with blood vessels that have leaked or ruptured. Haemorrhagic strokes account for 20% of all strokes. There are two main subtypes: Intracerebral haemorrhage (bleeding directly into the brain parenchyma) and subarachnoid haemorrhage (SAH – bleeding into the cerebrospinal fluid within the subarachnoid space that surrounds the brain). Risk factors for stroke include age (>55 years), race (African Americans and Asian individuals have a higher risk), male gender, high blood pressure, cigarette smoking, high cholesterol, diabetes, obstructive sleep apnoea, cardiovascular disease (including heart failure, abnormal heart rhythms such as atrial fibrillation), cocaine use, and personal or family history of stroke/TIA/heart attack,. Symptoms of a stroke include trouble speaking and/or understanding what others are saying, paralysis or numbness of the face, arm or leg, vision problems, headache, or difficulty walking. The acronym FAST (face, arms, speech, time) can be used to assess for signs and symptoms of a stroke. Initial assessment should include history, physical examination, glucose level, oxygen saturation, and non-contrast CT brain or brain MRI. Ischaemic stroke management may include thrombolysis (within 4.5 hours of symptom onset), or mechanical thrombectomy (due to a large artery occlusion in the anterior circulation), antithrombotic therapy using aspirin, DVT prophylaxis, lipid lowering therapy, blood pressure reduction, and behavioural/lifestyle

changes. The main indicator for oral anticoagulation following an ischaemic stroke is atrial fibrillation.

Intracranial haemorrhage management varies depending on the cause, but may involve reversal of anticoagulation, blood pressure management, and/or intracranial pressure management (e.g. CSF drainage, surgical decompression, osmotic therapy).

Patients with an acute stroke are reported to have better outcomes when admitted to a hospital unit that is specialized for the care of stroke patients.

Magnitude of signal

DPAR

The vaccine disproportionality analysis (DPAR) performed on data from March-June 2021 (see D21-3124789) flagged Vaxzevria and the following PT's:

- Vaxzevria - Cerebral haemorrhage: 12 cases in period, 12 cases total, 11 sole suspect. PRR 5.03, LCI 1.98
- Vaxzevria – Cerebral infarction: 14 cases in period, 14 cases total, all sole suspect. PRR 6.85. LCI 2.63.
- Vaxzevria – Cerebrovascular accident: 104 cases in period, 104 cases total, 102 sole suspect. PRR 7.27. LCI 5.08.
- Vaxzevria – Haemorrhage intracranial: 6 cases in period, 6 cases total, all sole suspect. PRR 5.87, LCI 2.01.
- Vaxzevria – SAH: 5 cases in period, 5 cases total, all sole suspect. PRR 14.68. LCI 1.72.
- Vaxzevria – Ischaemic stroke: 10 cases in period. 10 cases total. All sole suspect. PRR 5.87. LCI 2.01.
- Vaxzevria – TIA: 32 cases in period, 32 cases total. 30 sole suspect. PRR 5.87. LCI 3.22.

No 'cerebrovascular accident' related PT's flagged on the March-June 2021 DPAR for Comirnaty (see D21-3124789).

O/E Analysis

O/E analysis for X vaccine and Y signal			
Risk window	**Observed cases**	**Expected cases**	**O/E ratio (95% CI)**
X days			
Comment	Observed is greater than/less than/meeting expected. If the CI doesn't include one, this can be described as 'significantly greater than' or 'significantly less than'		
Y days			
Comment	Observed is greater than/less than/meeting expected. If the CI doesn't include one, this can be described as 'significantly greater than' or 'significantly less than		
AIR data to DATE/MONTH/YEAR; AEMS data to DATE/MONTH/YEAR			

Commented s22 [redacted] - note that we are awaiting an O/E analysis from VERA, however this finding is unlikely to change the current recommendation as further analysis of this potential signal is required.

PTs searched in AEMS:

TTO information for cases, was it used to refine AEMS cases?

If TTO was unknown, were these cases included?

Were case definitions used to refine AEMS case numbers?

B/G rate used and source

Signal	Vaccine name	Observed cases	Expected cases (7-Day risk window)	Expected cases (14-Day risk window)
Reaction X	Vaccine A			
	Vaccine B			

No. of AEFI reports

A search of the AEMS database was performed using Qlik – COVID-19 vaccine surveillance platform on 22 November 2021. Separate searches were performed to investigate for ischaemic and haemorrhagic strokes.

The SMQ search 'Ischaemic central nervous system vascular conditions' was used which includes the following PT's: cerebrovascular accident, transient ischaemic attack, cerebral infarction, ischaemic stroke, retinal artery occlusion, cerebral thrombosis, lacunar infarction, cerebral venous thrombosis, embolic stroke, cerebral artery thrombosis, brain stem infarction, cerebellar stroke, thalamic infarction, amaurosis fugax, carotid artery thrombosis, cerebellar infarction, cerebral ischaemia, thrombotic stroke, vertebral artery occlusion, brain stem stroke, carotid artery occlusion, carotid artery stenosis, vertebrobasilar insufficiency, basal ganglia stroke, basilar artery occlusion, brain hypoxia, cerebellar artery thrombosis, cerebral artery stenosis, cerebral small vessel ischaemic disease, cerebrovascular disorder.

A total **of 612 'Ischaemic central nervous system vascular conditions'** reports were identified – **461 related to Vaxzevria, 145 related to Comirnaty, 5 'COVID-19 vaccine trade name not specified', and 3 related to Spikevax** (Moderna – Elasomeran). See D21-3357793 (Qlik dashboard display).

A second search was performed using SMQ search 'Haemorrhagic central nervous system vascular conditions' which includes the following PT's: cerebrovascular accident, cerebral haemorrhage, haemorrhage, haemorrhage intracranial, subarachnoid haemorrhage, subdural haematoma, haemorrhagic stroke, subdural haemorrhage, basal ganglia haemorrhage, cerebellar stroke, ruptured cerebral aneurysm, brain stem haemorrhage, brain stem stroke, haemorrhagic transformation stroke, basal ganglia stroke, cerebellar haemorrhage, cerebral haematoma, cerebrovascular disorder, extradural haematoma, extradural haematoma evacuation, haemorrhagic cerebral infarction, intraventricular haemorrhage, subdural haematoma evacuation, thalamus haemorrhage, vertebrobasilar stroke.

A total of **464 'Haemorrhagic central nervous system vascular conditions' reports were identified – 351 related to Vaxzevria, 106 related to Comirnaty, 5 related to Spikevax (Moderna – Elasomeran), and 3 related to**

	'COVID-19 vaccine trade name not specified'. See D21-3357781 (Qlik dashboard display).

Summary of AEFI reports	**ISCHAEMIC central nervous system vascular conditions SMQ**
	
	Vaxzevria – PCDs at D21-3357841.
	
	• The **461 reports** included 261 cerebrovascular accident, 84 transient ischaemic attack, 25 cerebral infarction, 20 ischaemic stroke, 11 retinal artery occlusion, 11 lacunar infarction, 7 cerebral thrombosis, 6 cerebral artery thrombosis, 6 cerebral venous thrombosis, 4 brain stem infarction, 4 cerebellar stroke, 3 carotid artery thrombosis, 3 cerebellar infarction, 3 cerebral ischaemia, 3 embolic stroke, 3 thrombotic stroke, 3 vertebral artery occlusion, 2 amaurosis fugax, 2 carotid artery occlusion, 2 carotid artery stenosis, 2 thalamic infarction, 2 vertebrobasilar insufficiency, 1 basilar artery occlusion, 1 cerebellar artery thrombosis, 1 cerebral artery stenosis, 1 cerebral small vessel ischaemic disease, 1 embolic cerebellar infarction, 1 lacunar stroke, 1 reversible cerebral vasoconstriction syndrome, 1 spinal artery thrombosis, 1 spinal cord infarction, 1 spinal cord ischemia, 1 vertebrobasilar stroke, and 1 white matter lesion.
	• 51.2% of reports occurred in males
	• The majority of reports occurred in individuals aged 75 years and above (197 reports), 65-74 years (137 reports), 45-64 years (101 reports), then 18-44 year olds (11 reports). 15 reports were in individuals of unknown age.
	• s22 [redacted]
	• Most reports occurred following dose 1 (298 reports) then dose 2 (72 reports).
	• 43 cases had a hospital admission. 13 cases had a hospital ED presentation. 1 case managed by GP. 1 had a nurse assessment.
	• 158 were classified as not recovered/not resolved/ongoing, 49 recovered/resolved, 5 recovered/resolved with sequelae, and 80 recovering/resolving.
	• Note the following TTS classifications as per case narratives:
	  ○ 5 confirmed TTS cases (s22 [redacted] s22 [redacted]
	  ○ 2 cases of probable TTS (s22 [redacted] s22 [redacted]
	  ○ 5 cases under investigation for possible TTS (s22 [redacted] s22 [redacted]
	  ○ 10 cases unlikely TTS (s22 [redacted] - s22 [redacted]
	  ○ 4 case reviewed and dismissed as being TTS (s22 [redacted] s22 [redacted]
	• **42 reports were fatal**
	  ○ Ages of fatal reports ranged from 18-100 years
	  ○ 52.4% of fatal cases occurred in females
	  ○ Coded as follows: 32 CVA, 5 cerebral infarction, 2 cerebral artery thrombosis, 1 carotid artery thrombosis, 1 cerebellar infarction,

1 cerebral thrombosis, 1 cerebral venous thrombosis, 1 lacunar infarction, and 1 vertebrobasilar stroke.
    - No individuals were reported as residents of nursing homes/aged care facilities.
    - Note the following as per case narratives: 1 confirmed TTS case (s22), 1 case of probable TTS (s22 s22 1 case under investigation for possible TTS (s22 s22 3 cases unlikely TTS and 1 case reviewed and dismissed as TTS.
    - Note that the case narrative of 1 report (s22) states the case was not fatal and was discharged to residential care (ADR Reports notified by email of this possible coding error).

Comirnaty - PCDs at D21-3357861

- The **145 reports** included 81 cerebrovascular accident, 28 transient ischaemic attack, 7 cerebral infarction, 7 ischaemic stroke, 5 cerebral thrombosis, 4 embolic stroke, 3 retinal artery occlusion, 2 brain stem stroke, 2 thalamic infarction, 1 amaurosis fugax, 1 basal ganglia stroke, 1 brain hypoxia, 1 cerebral venous thrombosis, 1 cerebrovascular disorder, 1 hypoxic-ischaemic encephalopathy, 1 lacunar infarction, 1 thrombotic stroke.
- 53.1% of reports occurred in females
- The majority of reports occurred in individuals aged 45-64 years years (43 reports), 75 years and above (40 reports), 18-44 year olds (39 reports), 65-74 years (13 reports), then 1 adolescent (13 years). 15 reports were in individuals of unknown age.
- s22
- Most reports occurred following dose 1 (68 reports) then dose 2 (49 reports).
- 47 cases had a hospital admission. 42 cases had a hospital ED presentation. 12 managed by GP. 2 had a nurse assessment.
- 44 were classified as not recovered/not resolved/ongoing, 17 recovered/resolved, 1 recovered/resolved with sequelae, and 19 recovering/resolving.
- **25 reports were fatal**
    - Ages of fatal reports ranged from 19-95 years; majority in 75 and above age group (14 reports)
    - 64% of fatal cases occurred in females
    - Coded as follows: 19 CVA, 2 ischaemic stroke, 1 brain hypoxia, 1 cerebral infarction, 1 cerebrovascular disorder, 1 hypoxic-ischaemic encephalopathy, and 1 thrombotic stroke.
    - 12 individuals were residents of nursing homes/aged care facilities
    - It is noted that the case narratives do not state that the vaccine was suspected of being causally associated with the reported deaths.

Spikevax – PCDs at D21-3357874

- **The 3 reports** were all coded as cerebrovascular accident.
- 66.7% of reports occurred in females

- Ages of cases were 39, 52, and 54 years.
- s22 [redacted]
- 1 report occurred following dose 1. The dose number of the 2 other reports were not stated.
- All 3 cases had a hospital admission.
- No fatal cases.
- **Note that 2 of these cases s22 [redacted] and s22 [redacted] s22 [redacted] may be duplicates (email notification sent to ADR reports of this possible case duplication)

HAEMORRHAGIC central nervous system vascular conditions SMQ

Vaxzevria – PCDs at D21-3357785

- The **351 reports** included 262 CVA, 28 cerebral haemorrhage, 17 haemorrhage intracranial, 12 subarachnoid haemorrhage, 12 subdural haematoma, 6 haemorrhagic stroke, 4 cerebellar stroke, 4 subdural haemorrhage, 3 basal ganglia haemorrhage, 3 ruptured cerebral aneurysm, 2 brain stem haemorrhage, 2 haemorrhagic transformation stroke, 1 cerebral haematoma, 1 extradural haematoma, 1 extradural haematoma evacuation, 1 haemorrhagic cerebral infarction, 1 intraventricular haemorrhage, 1 subdural haematoma evacuation, 1 thalamus haemorrhage, and 1 vertebrobasilar stroke.
- 50.4% of reports occurred in males
- The majority of reports occurred in individuals aged 75 years and above (152 reports), 65-74 years (107 reports), 45-64 years (70 reports), then 18-44 year olds (10 reports). 12 reports were in individuals of unknown age.
- Most reports occurred following dose 1 (209 reports). Some (67 reports) occurred following dose 2. The remaining reports did not state dose number.
- s22 [redacted]
- 200 cases had a hospital admission. 73 cases had a hospital ED presentation. 15 managed by GP. 1 had a nurse assessment.
- 124 were classified as not recovered/not resolved/ongoing, 22 recovered/resolved, 3 recovered/resolved with sequelae, and 63 recovering/resolving.
- Note the following TTS classifications as per case narratives:
  - 13 confirmed TTS cases (s22 [redacted] s22 [redacted])
  - 3 cases of probable TTS (s22 [redacted] s22 [redacted])
  - 6 cases under investigation for possible TTS (s22 [redacted] s22 [redacted])
  - 4 cases unlikely TTS (s22 [redacted] s22 [redacted])

- 6 cases reviewed and dismissed as being TTS s22 s22

- **65 reports were fatal**
  - Ages of fatal reports ranged from 34-100 years
  - 56.9% of fatal cases occurred in females
  - Coded as follows: 32 CVA, 9 cerebral haemorrhage, 8 haemorrhage intracranial, 6 subarachnoid haemorrhage, 4 subdural haematoma, 1 basal ganglia haemorrhage, 1 brain stem haemorrhage, 1 cerebral haematoma, 1 extradural haematoma, 1 extradural haematoma evacuation,1 haemorrhagic stroke, 1 haemorrhagic transformation stroke, 1 intraventricular haemorrhage, 1 ruptured cerebral aneurysm, 1 subdural haematoma evacuation, 1 subdural haemorrhage, and 1 vertebrobasilar stroke.
  - 1 individual was a resident of a nursing homes/aged care facility.
  - Note the following as per case narratives: 6 confirmed TTS case (s22 s22 - s22 , no cases of probable TTS, 1 case under investigation for possible TTS (s22 s22), 2 cases unlikely TTS (s22 s22 and 2 cases reviewed and dismissed as TTS s22).

Comirnaty – PCDs at D21-3357789

- The **106 reports** included 82 CVA, 11 cerebral haemorrhage, 4 haemorrhage intracranial, 4 subarachnoid haemorrhage, 2 basal ganglia haemorrhage, 2 brain stem stroke, 2 haemorrhagic stroke, 2 subdural haemorrhage, 1 basal ganglia stroke, 1 cerebellar haemorrhage, 1 cerebrovascular disorder, 1 ruptured cerebral aneurysm, 1 subdural haematoma.
- 57.5% of reports occurred in females
- The majority of reports occurred in individuals 45-64 years (34 reports), 75 years and above (32 reports), 18-44 years (24 reports), 65-74 years (9 reports), in individuals of unknown age (6 reports), and 1 in an adolescent (13 years).
- Most reports occurred following dose 1 (49 reports), compared to dose 2 (43 reports).
- s22
- 30 cases had a hospital admission. 32 cases had a hospital ED presentation. 8 managed by GP. 1 had a nurse assessment.
- 31 were classified as not recovered/not resolved/ongoing, 4 recovered/resolved, 0 recovered/resolved with sequelae, and 13 recovering/resolving.
- **24 reports were fatal**
  - Ages of fatal reports ranged from 39-93 years
  - 58.3% of fatal cases occurred in females
  - Coded as follows: 19 CVA, 4 cerebral haemorrhage, 2 haemorrhage intracranial, 2 subarachnoid haemorrhage, 1 cerebrovascular disorder, and 1 ruptured cerebral aneurysm.

	○ 7 individuals were residents of a nursing homes/aged care facility. **Spikevax** – PCDs at D21-3357790 • The **5 reports** included 3 CVA, 1 haemorrhagic stroke, and 1 subdural haematoma. • 80% of reports occurred in females • The majority of reports occurred in individuals 45-64 years (3 reports), then 1 report in 18-44 years and 1 report in 65-74 year cohorts. • Most reports occurred following dose 1 (2 reports), and 1 report following dose 2. • s22 [redacted] • cases had a hospital admission. cases had a hospital ED presentation. managed by GP. had a nurse assessment. • Investigations included (angiogram), cardiac telemetry incl ECGs, transthoracic echocardiogram. • Treatment reported to include: • were classified as not recovered/not resolved/ongoing, recovered/resolved, recovered/resolved with sequelae, and recovering/resolving. • No fatal cases **Overlapping cases** **Note that the following were included in both ischaemic and haemorrhagic searches: 349 CVA, 4 cerebellar stroke, 2 brain stem stroke, 1 basal ganglia stroke, 1 cerebrovascular disorder, and 1 vertebrobasilar stroke.

4. Regulatory surveillance

Local, including: PI, Sponsor's PSUR/MSSR, and applicable clinical guidance	**Product Information (PI)** **Vaxzevria** Stroke/CVA is not included in the Australian PI for Vaxzevria (revised 25 October 2021). However the PI does include reference to thrombosis and thrombocytopenia syndrome (TTS) which may be accompanied by bleeding and *'include cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis... as well as arterial thrombosis concomitant with thrombocytopenia. The majority of the events occurred within the first 21 days following vaccination but have also been reported after this period. Some events had a fatal outcome.'*; see D21-3383610. **Comirnaty** Stroke/CVA is not included in the Australian PI for Vaxzevria (revised 25 October 2021) ; see D21-3383601. **Applicable clinical guidance** ATAGI Clinical guidance on use of COVID-19 vaccine in Australia (Version 7.4, dated 29 October 2021) includes the following reference to stroke/CVA; see D21-3383662.

- Conditions associated with increased risk of severe COVID-19: … chronic neurological conditions including stroke
- Precautionary conditions for Vaxzevria: There is no evidence that a past history of clots or of any clotting tendencies increases the risk of TTS and people with the following conditions can receive Vaxzevria…. History of ischaemic heart disease or stroke.

Sponsor's PSUR/MSSR/SSR

Vaxzevria

The MSSR for Vaxzevria (1 August 2021 to 30 September 2021; see D21-3260098) lists the following PT's for AESI including 'embolic and thrombotic events (thrombosis)' – see Page 4099 of the MSSR. Of note, this group includes ischaemic and haemorrhagic stroke terms such as ischaemic cerebral infarction, ischaemic stroke, haemorrhagic stroke, haemorrhagic infarction, and haemorrhagic transformation stroke. However, this grouping includes a wide range of non-stroke terminology such as mesenteric arteriosclerosis, pulmonary artery occlusion, iliac vein occlusion, and disseminated intravascular coagulation.

An O/E analysis for 'embolic and thrombotic events' is provided. A total of 8,775 observed cases were reported, and 70,326.22 cases expected, using a risk period of 28 days and background rate of 391.08 per 100,000 person years. Age and gender stratified analysis shows observed significantly less than expected for all groups.

Cumulative totals of reports for events coded under the higher level term (HLT) 'Central nervous system haemorrhages and cerebrovascular accidents' (total 4,904 events) is included in the MSSR, including: 2 basal ganglia stroke, 34 brain stem infarction, 13 brain stem stroke, 3 cerebellar artery thrombosis, 27 cerebellar infarction, 28 cerebellar stroke, 28 cerebral artery embolism, 16 cerebral artery occlusion, 42 cerebral artery thrombosis, 389 cerebral infarction, 65 cerebral ischaemia, 1 cerebral microembolism, 2 cerebral microinfarction, 201 cerebral thrombosis, 3 cerebral vascular occlusion, 2072 cerebrovascular accident, 2 embolic cerebellar infarction, 5 embolic cerebral infarction, 41 embolic stroke, 13 haemorrhagic cerebral infarction, 99 haemorrhagic stroke, 17 haemorrhagic transformation stroke, 53 ischaemic cerebral infarction, 577 ischaemic stroke, 30 lacunar stroke, 2 spinal stroke, 1 stroke in evolution, 24 thrombotic stroke, 5 vertebral artery occlusion, 7 vertebral artery thrombosis, 11 vertebrobasilar stroke, 1 spinal artery thrombosis, 936 transient ischaemic attack. Numbers of interval cases in this category, classified as medical or non-medically confirmed, and stratified by age, are provided.

An O/E for the above 'Central nervous system haemorrhages and cerebrovascular accidents' terms is not provided in the MSSR. There is therefore no specific O/E analysis or discussion regarding the specific risk of stroke (ischaemic or haemorrhagic) following Vaxzevria administration.

Comirnaty

The MSSR for Comirnaty (1 October 2021 to 31 October 2021; see D21-3349826) lists 'Stroke' as an AESI category. Events coded under the HLT 'Central nervous system haemorrhages and cerebrovascular accidents' or HLT 'Cerebrovascular venous and sinus thrombosis' are included in this category. A total of 609 cases are reported to date, of which 304 are medically confirmed and 305 are non-

	medically confirmed. The majority of events are reported in males (304 cases), and adults (305 cases). The most frequently reported PT's for ischaemic stroke included: cerebrovascular accident (234 cases), ischaemic stroke (82 cases), cerebral thrombosis (28 cases), cerebral venous thrombosis (20 cases), cerebral ischaemic (14 cases), brain stem infarction (9 cases), cerebellar infarction (9 cases), embolic stroke (6 cases), thalamic infarction (6 cases), carotid artery thrombosis (5 cases), and transverse sinus thrombosis (5 cases). The most frequently reported PT's for haemorrhagic stroke included: cerebral haemorrhage (61 cases), subarachnoid haemorrhage (24 cases), haemorrhagic stroke (18 cases), haemorrhage intracranial (6 cases), and cerebral haematoma (5 cases). An O/E analysis was performed as follows: • Haemorrhagic stroke (PT's including: Brain stem haemorrhage, Cerebral haematoma, Cerebral haemorrhage, Haemorrhage intracranial, haemorrhagic stroke, intracranial haematoma, and Subarachnoid haemorrhage) o Using all cases and 21- and 42-day risk windows, observed was significantly less than expected (0.033, 95% CI 0.031-0.035; and 0.025, 95% CI 0.024-0.027). o Age stratified O/E analysis showed observed less than expected in all groups. o Background rate used: 44.72 per 100,000 person years o Age stratified rates: <17 years: 1.40; 18-24 years: 2.05; 25-49 years: 7.96; 50-59 years: 31.77; 60-69 years: 62.32; 70+ years: 140.23 per 100,00 person years. • Ischaemic stroke (PT's including: Basal ganglia infarction, basal ganglia stroke, Basilar artery thrombosis, brain stem stroke, Cerebral infarction, Cerebral thrombosis, Cerebral venous sinus thrombosis, Cerebrovascular accident, ischaemic stroke, Lacunar infarction, pituitary infarction, and Thrombotic stroke) o Using all cases and 21- and 42-day risk windows, observed was significantly less than expected (0.025, 95% CI 0.025-0.026; and 0.020, 95% CI 0.019-0.020). o Age stratified O/E analysis showed observed less than expected in all groups. o Background rate used: 237.40 per 100,000 person years o Age stratified rates: <17 years: 1.93; 18-24 years: 5.27; 25-49 years: 18.96; 50-59 years: 81.86; 60-69 years: 201.00; 70+ years: 482.58 per 100,00 person years. Note that the background rates referenced in the Comirnaty MSSR were derived from the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCEPP) which utilise the ACCESS background rates of AESI for COVID-19 vaccines. The ES_SIDIAP_PCHOSP (Spain-Catalunya primary care, data reported from specialists, and hospital diagnoses) rates were utilised for haemorrhagic stroke rates and IT_ARS (Italy hospitalisation and emergency department discharge diagnoses) were used for ischaemic stroke rates. See https://vac4eu.org/covid-19-tool/.
US FDA	**Label**

	Vaxzevria Note that Vaxzevria is not currently provisionally registered in the United States. **Comirnaty** The US FDA label for Comirnaty (revised 11/2021; document ID 9b17a287-f8d1-4c45-ab63-a8943edb244c; version 25) does not include reference to stroke/CVA. **Relevant regulatory action** The current COVID-19 vaccine recommendations from the Advisory Committee on Immunisation Practices (ACIP) do not reference stroke in relation to Comirnaty.
EU EMA	**Summary of Product Characteristics (SmPC)** **Vaxzevria** The EMA SmPC for Vaxzevria (last updated 24/11/2021) does not include reference to stroke/CVA. However, the SmPC does include the following information in relation to 'Cerebrovascular venous and sinus thrombosis' under Section 4.4 Special warnings and precautions for use: *'Events of cerebrovascular venous and sinus thrombosis without thrombocytopenia have been observed very rarely following vaccination with Vaxzevria. Some cases had a fatal outcome. The majority of these cases occurred within the first four weeks following vaccination. This information should be considered for individuals at increased risk for cerebrovascular venous and sinus thrombosis. These events may require different treatment approaches than TTS and healthcare professionals should consult applicable guidance.'* Section 4.8 Undesirable effects, Table 1 Adverse drug reactions also lists 'Cerebrovascular venous and sinus thrombosis', with a frequency of 'not known'. **Comirnaty** The EMA SmPC for Comirnaty (last updated 25/11/2021) does not include reference to stroke/CVA. **Relevant regulatory action** **Vaxzevria** The Vaxzevria COVID-19 vaccine safety update from 11 November 2021 (see D21-3385040) states that 'Cerebrovascular venous and sinus thrombosis (CVST) will be added to the PI as a side effect of Vaxzevria. The Vaxzevria COVID-19 vaccine safety updates from 6 October, 8 September, 11 August, 14 July, and 18 June do not reference to stroke/CVA. EMA PRAC meeting highlights from 25-28 October, 27-30 September, 30 August-2 September, 5 August, 5-8 July, and 7-10 June 2021 do not include reference to stroke/CVA and Vaxzevria. **Comirnaty**

	The Comirnaty COVID-19 vaccine safety updates from 11 November 2021, 6 October, 8 September, 11 August, 14 July, and 18 June do not reference stroke/CVA. EMA PRAC meeting highlights from 25-28 October, 27-30 September, 30 August-2 September, 5 August, 5-8 July, and 7-10 June 2021 do not include reference to stroke/CVA and Comirnaty.
UK MHRA	**Summary of Product Characteristics (SPC)**
	Vaxzevria The SPC for Vaxzevria (revised 14/10/2021) does not include reference to stroke/CVA. However, the SPC does reference 'Thrombosis with thrombocytopenia and coagulation disorders' under Section 4.4 Special warnings and precautions. **Comirnaty** The SPC for Comirnaty (revised 10/11/2021) does not include reference to stroke/CVA.
	Relevant regulatory action
	The MHRA Coronavirus vaccine – weekly summary of Yellow Card reporting' (updated 26 November 2021) references 'thrombo-embolic (blood clotting) events with concurrent low platelets (see D21-3385127). The following is specifically noted, *'The MHRA has also confirmed that the evidence to date does not suggest that the COVID-19 vaccine AstraZeneca causes venous thromboembolism which occurred in the absence of a low platelet count'.*
Health Canada	**Product Monograph**
	Vaxzevria The product monograph for Vaxzevria (last revised November 19, 2021; submission control number 253700) does not reference stroke/CVA. However, the product monograph does reference 'Thrombosis and thrombocytopenia' under Section 7 Warnings and precautions and 8.3 Post-market adverse reactions. **Comirnaty** The product monograph for Comirnaty (last revised November 19, 2021; submission control number 257698) does not reference stroke/CVA.
	Relevant regulatory action
	Nil to date.
NZ Medsafe	**Datasheet**
	Vaxzevria The datasheet for Vaxzevria (last revised 5 November 2021) does not include reference to stroke/CVA. However, the datasheet does include the risk of

	'thrombosis and thrombocytopenia including thrombosis with thrombocytopenia syndrome (TTS)'. **Comirnaty** The datasheet for Comirnaty (last revised 8 November 2021; version pfdcovii11121) does not include reference to stroke/CVA.
	Relevant regulatory action
	Nil to date.
Other international regulators (via ICMRA PV Network and ACCESS)	**ICMRA PV network:** stroke/CVA not discussed in the ICMRA meeting on 16 November, 21 September, or 6 September.
	s33
	EMA Pandemic Taskforce COVID-ETF: stroke/CVA not discussed in meeting on 18 November and 21 October 2021. **CHMP:** stroke/CVA not discussed in meeting on 25 November and 25 October 2021. See relevant notes in E21-305947

5. Other information

s33

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Document 3

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Literature	**The following article by Hippisley-Cox prompted inclusion of Comirnaty in TIP:**
	
	Hippisley-Cox et al. August 2021. Risk of thrombocytopenia and thromboembolism after COVID-19 vaccination and SARS-CoV-2 positive testing: self-controlled case series study. BMJ. D21-3335135 and supplementary data at D21-3335884.
	
	• Self-controlled case series study using national data from the United Kingdom on COVID-19 vaccination and hospital admissions. Patient level data from approximately 30 million vaccinated people in England between 1 December 2020 and 24 April 2021 was utilised.
	• Cases were identified using hospital inpatient admissions with International Classification of Disease version 10 (ICD-10) codes in their first 13 diagnoses fields that indicated an outcome of interest.
	• As per the supplementary data, the arterial thromboses studied were:
	  o I74 - Arterial embolism and thrombosis
	  o I740 - Embolism and thrombosis of abdominal aorta
	  o I741 - Embolism and thrombosis of other and unspecified parts of aorta
	  o I742 - Embolism and thrombosis of arteries of upper extremities
	  o I743 - Embolism and thrombosis of arteries of lower extremities
	  o I744 - Embolism and thrombosis of arteries of extremities, unspecified
	  o I745 - Embolism and thrombosis of iliac artery
	  o I748 - Embolism and thrombosis of other arteries
	  o I749 - Embolism and thrombosis of unspecified artery
	• As per the supplementary data, the ischaemic strokes studied were:
	  o G45 - Transient cerebral ischaemic attacks and related syndromes
	  o G450 - Vertebrobasilar artery syndrome
	  o G451 - Carotid artery syndrome (hemispheric)
	  o G452 - Multiple and bilateral precerebral artery syndromes
	  o G453 - Amaurosis fugax
	  o G454 - Transient global amnesia
	  o G458 - Other transient cerebral ischaemic attacks and related syndromes
	  o G459 - Transient cerebral ischaemic attack, unspecified
	  o I63 - Cerebral infarction
	  o I630 - Cerebral infarction due to thrombosis of precerebral arteries
	  o I631 - Cerebral infarction due to embolism of precerebral arteries
	  o I632 - Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries

	o I633 - Cerebral infarction due to thrombosis of cerebral arteries o I634 - Cerebral infarction due to embolism of cerebral arteries o I635 - Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries o I636 - Cerebral infarction due to cerebral venous thrombosis, non-pyogenic o I638 - Other cerebral infarction o I639 - Cerebral infarction, unspecified o I64 - Stroke, not specified as haemorrhage or infarction o I64X - Stroke, not specified as haemorrhage or infarction • Cases reported were following first dose of either Vaxzevria, Comirnaty, or a positive SARS-CoV-2 test. • Primary outcomes reported included o Thrombocytopenia: increased risk at ▪ 8-14 days after Vaxzevria: incidence rate ratio (IRR) 1.33, 95% CI 1.19 to 1.47; and at 22-28 days after Vaxzevria: IRR 1.26, 95% CI 1.13 to 1.42 ▪ 1-7 days after positive a positive SARS-CoV-2 test: IRR 14.04, 95% CI 12.08 to 16.31. o Venous thromboembolism: increased risk at ▪ 8-14 days following Vaxzevria; IRR 1.10, 95% CI 1.02 to 1.18. ▪ 8-14 days after a positive SARS-CoV-2 test: IRR 13.86, 95% CI 12.76 to 15.05. o Arterial thromboembolism: increased risk at ▪ 15-21 days following Comirnaty: IRR 1.06, 95% CI 1.01 to 1.10 ▪ 1-7 days after positive a SARS-CoV-2 test: IRR 6.55, 95% CI 6.12 to 7.02. • Secondary analyses found included o Cerebral venous sinus thrombosis (CVST): increased risk at ▪ 8-14 days following Vaxzevria: IRR 4.01, 95% CI 2.08 to 7.71 ▪ 8-14 days following Comirnaty: IRR 3.58, 95% CI 1.39 to 9.27. ▪ After positive SARS-CoV-2 test 8-14 days: IRR 13.43, 95% CI 1.99 to 90.59. o Increased risk of ischaemic stroke ▪ 15-21 days after Comirnaty: IRR 1.12, 95% CI 1.04 to 1.20. ▪ 1-7 days after positive SARS-CoV 2 test: IRR 3.94, 95% CI 3.46 to 4.47. Note SARS-CoV 2 test IRR greater than 1 out to 28 days (1.26). o Other rare arterial thrombotic events: increased risk ▪ 8-14 days after Vaxzevria: IRR 1.21, 95% CI 1.02 to 1.43. ▪ 8-14 days after a positive SARS-CoV-2 test: IRR 5.61, 95% CI 4.13 to 7.61. • Increased risk of co-occurrence of thrombocytopenia and venous thromboembolism within 8-14 days following Vaxzevria (IRR 1.34, 95% CI 0.99 to 1.83). No association of co-occurrence of thrombocytopenia and venous thromboembolism and Comirnaty. • Increased risk of co-occurrence of thrombocytopenia and arterial thromboembolism within 8-14 days of Comirnaty (IRR 1.40, 95% CI 0.97

to 2.01). No association of co-occurrence of thrombocytopenia and arterial thromboembolism and Vaxzevria.

- **Report estimates an excess 107 events of thrombocytopenia, 66 events of venous thromboembolism, and 7 events of CVST per 10 million doses of Vaxzevria.**
- **Report estimates an excess 143 cases of ischaemic stroke per 10 million doses of Comirnaty.**
- **Comparatively, the report estimates an excess of 934 cases of thrombocytopenia, 12,614 cases of venous thromboembolism, 1,699 cases of ischaemic stroke, and 20 cases of CVST per 10 million SARS CoV-2 positive tests.**
- **Authors conclude that the analysis shows a very small risk of clotting and other blood disorders following first dose COVID-19 vaccination. Whilst serious, the risk of these outcomes is much higher following infection with COVID-19.**
- This study therefore found elevated rates of some AEFI compared to background rates, however these rates were lower than events occurring with COVID-19 infection.

Literature search

A literature search was performed on 24 November 2021 using PubMed and keywords 'COVID-19 vaccin*' and 'stroke'.

The following articles were identified that discussed the **association between stroke and COVID-19 disease**:

- Zhai, P et al. 2020. The impact of COVID-19 on ischemic stroke. Diagnostic Pathology. D21-3368373
- Yu and Yu. 2020. Severe acute respiratory syndrome Coronavirus 2-induced neurological complications. Frontiers in Cell and Developmental Biology. D21-3368374
- Katsoularis I et al. 2021. Risk of acute myocardial infarction and ischaemic stroke following COVID-19 in Sweden: a self-controlled case series and matched cohort study. Lancet. D21-3368376
- Moore, P et al. 2021. Hypercoagulability of COVID-19 and neurological complications: a review. Journal of Stroke and Cerebrovascular Diseases. D21-3368377

The following articles were identified that discussed **stroke and COVID-19 vaccination:**

Al-Mayhuni et al. Ischaemic stroke as a presenting feature of ChAdOx-1 nCoV-19 vaccine induced immune thrombotic thrombocytopenia. D21-3368380

- Case series of 3 patients
  - A 35 year old female that developed an ischaemic stroke 6 days after Vaxzevria (dose not stated). Patient suffered brainstem death.
  - A 37 year old female that developed an ischaemic stroke 12 days after Vaxzevria (dose not stated).
  - 43 year old male developed an ischaemic stroke 21 days after Vaxzevria (dose not stated).
- Suggest that the neurological spectrum of VITT can include arterial occlusion, and that patients presenting with ischaemic stroke following

Vaxzevria should be evaluated for VITT with lab tests including platelet count, D-dimer, fibrinogen, and anti-PF4 antibodies.

Patone et al. 2021. Neurological complications after first dose of COVID-19 vaccines and SARS-CoV-2 infection. Nature Medicine. D21-3368382

- English National Immunisation (NIMS) database of COVID-19 vaccination was linked at the individual patient level to national data for mortality, hospital admissions, and SARS-Co-V-2 infection data to examine an association between 1st dose Vaxzevria, Comirnaty, and neurological complications including acute CNS demyelinating events, encephalitis meningitis and myelitis, GBS, bell's palsy, myasthenic disorders, haemorrhagic stroke, and subarachnoid haemorrhage. The study incorporated over 30 million people (20 million Vaxzevria recipients and 12 million Comirnaty recipients).
- A self-controlled case series methodology was utilised.
- Results
    - No association between Vaxzevria or Comirnaty and acute CNS demyelinating events, but increased risk associated with a positive SARS-CoV-2 test (IRR 19.34).
    - Trend towards increased risk of encephalitis, meningitis, and myelitis after Vaxzevria (IRR 1.32) and no association with Comirnaty. Increased risk of hospitalisation or death for this outcome with a positive SARS-CoV-2 test (IRR 38.57).
    - GBS – increased risk of hospital admission or death following Vaxzevria (IRR 2.90 at 15-21 days and IRR 2.21 at 22-28 days). No association with Comirnaty.
    - Bell's palsy: increased risk of hospitalisation for Bell's palsy after Vaxzevria (IRR 1.29). No association with Comirnaty.
    - Myasthenic disorder: increased risk of hospitalisation nor death for myasthenic disorder following Vaxzevvria (IRR 1.57). No association with Comirnaty.
    - Increased risk of hospitalisation or death from haemorrhagic stroke reported with Comirnaty at **1-7days – IRR 1.27**, 95% CI 1.02-1.59, and at **15-21 days – IRR 1.38,** 95% CI 1.12-1.71, and between **1-28 days - IRR 1.24,** 95% CI 1.07-1.43.
        - Risk reported to be significantly higher in female participants (P=0.007); IRR for haemorrhagic stroke in female participants was 1.44 (95% CI 1.05-1.96) at 1-7 days compared to 1.13 (9% CI 0.82-1.57) for males and at 15-21 days for females was 1.84 (95% CI 1.40-2.42) compared to 0.98 (95% 0.70-1.38) for males.
        - Note that the magnitude of the association was reduced in sensitivity analysis that accounted for fatal events.
        - The association between Comirnaty and haemorrhagic stroke was not replicated using Scottish data (IRR 0.65).
        - No association between haemorrhagic stroke and Vaxzevria.
        - Also an increased risk of haemorrhagic stroke up to 7 days after a positive SARS-CoV-2 test (IRR 12.42, 95% CI 7.73-19.95).
    - No increased risk of subarachnoid haemorrhage following Comirnaty or Vaxzevria.
- Estimated excess events (Supplementary Table 5)

	o 60 extra cases of haemorrhagic stroke per 10 million people vaccinated in the 1-28 days period after vaccination of Comirnaty. • Mechanisms for the increased risk of haemorrhagic stroke and Comirnaty may be an increased risk of immune thrombocytopenic purpura following mRNA vaccination, contributing to major bleeding events. • All neurological conditions were linked to SARS-CoV-2 infection – particularly an excess of inflammatory disorders. • Further validation of these findings are warranted. **Jabagi et al. 2021. Myocardia infarction, stroke, and pulmonary embolism after BN5162b2 mRNA COVID-19 vaccine in people aged 75 years or older. JAMA.** D21-3368383 • Population based study using the French National Health Data System linked to the national COVID-19 vaccination database. • Self controlled case series method utilised • No increase in the incidence of AMI, stroke (ischaemic or haemorrhagic) or PE was detected 14 days following Comirnaty. **Alammar, M. 2021. Ischemic stroke after AstraZeneca (COVID-19) vaccination. Saudi Medical Journal.** D21-3368378 • Case report of a 43-year-old male that developed an ischaemic stroke 3 days following 1st dose of Vaxzevria. • Patients with severe COVID-19 infection are at increased risk of developing ischemic stroke, other arterial and venous thromboembolisms because of high grade inflammatory response seen in severe SARS COV-2 infection developing a hypercoagulable state • This case does not fit the known vaccine induced prothrombotic immune thrombocytopenia following Vaxzevria as the patient had normal platelet counts. **Markus, H. 2021. Ischaemic stroke can follow COVID-19 vaccination but is much more common with COVID-19 infection itself.** D21-3368379 • Editorial commentary regarding thrombotic complications occurring as part of COVID-19 related vaccine-induced immune thrombotic thrombocytopaenia (VITT) which can include ischaemic stroke as well as cerebral venous thrombosis. **Correa et al. 2021. Neurological symptoms and neuroimaging alterations related with COVD-19 vaccine: cause or coincidence? Clinical Imaging.** D21-3368381 • Case series of 3 patients with neurological symptoms temporally associated with Vaxzevria – one patient had an ischaemic stroke 2 days post-vaccination, one facial nerve palsy 7 days post-vaccination, and one had cervical myelitis. • In relation to the case of ischaemic stroke, the patient may have presented a form of vaccine-induced thrombosis without thrombocytopenia, as occurred in a case reported by Walter et al **De Melo Silva et al. 2021. Large haemorrhagic stroke after ChAdOx1 nCoV-19 vaccination: a case report. Acta Neurol Scand.** D21-3368395

	• Case report of 57yo female that developed a large deep frontal lobe parenchymal haematoma, 5 days following first dose Vaxzevria. **Kenda et al. 2021. Treatment of ChAdOx 1 nCoV-19 vaccine-induced immune thrombotic thrombocytopenia related acute ischaemic stroke. J Stroke Cerebrovasc Dis.** D21-3368396 • Case report of a 51yo female that developed acute left middle cerebral artery occlusion 7 days after the first dose of Vaxzevria.
Biological plausibility	As commented in Al-Mayhuni et al. (2021), ischaemic and haemorrhagic strokes following Vaxzevria administration may occur as part of spectrum of vaccine induced thrombosis and thrombocytopenia (VITT). Patone et al. (2021), report that a possible mechanism for the increased risk of haemorrhagic stroke and Comirnaty may be an increased risk of immune thrombocytopenic purpura following mRNA vaccination, contributing to major bleeding events.

s22 [redacted]

6. Conclusion

Conclusion	s33 [redacted] Specifically, the Australian sponsors for Comirnaty and Vaxzevria are requested to provide a review of ischaemic and haemorrhagic stroke, including an observed versus expected analysis. This analysis should include a discussion regarding the preferred terms (PT's) included and excluded, the background rates utilised, and an age and gender stratified analysis. The analysis provided by the Australian sponsors for Comirnaty and Vaxzevria should be sent to Evaluation stream for review. The purpose of this review would be to determine the appropriateness of current risk minimisation activities (e.g. whether a PI update is required). The PT's for stroke should also be considered and additional PT's may be added to the current AESI mapping list, or could be subdivided into ischaemic and haemorrhagic stroke AESI.
Proposed action	☒**Refer to Stream B – MAVIS Evaluation Stream**

<table>
<tr><td></td><td colspan="2">☐Refer to Stream C – Regulatory Outcomes Stream (ROS)

☐Refer to <Other>

☐Routine monitoring</td></tr>
<tr><td>Instructions for Stream B, MAVIS Evaluation Stream (if applicable)</td><td colspan="2">Evaluate the requested ischaemic and haemorrhagic stroke analysis that is to be provided by the Australian sponsors for Comirnaty and Vaxzevria. The review should also take into consideration the Australian rates and observed versus expected numbers of ischaemic and haemorrhagic stroke cases. The purpose of this review would be to determine the appropriateness of current risk minimisation activities (e.g. whether a PI update is required).</td></tr>
<tr><td rowspan="11">Instructions for Stream C, ROS (if applicable)</td><td colspan="2">Proposed regulatory action</td></tr>
<tr><td>☐PI/CMI update</td><td>☐Recall</td></tr>
<tr><td>☐Safety alert</td><td>☐IPMST topic</td></tr>
<tr><td>☐Medicines Safety Update (MSU)</td><td>☐Pregnancy Category update</td></tr>
<tr><td>☐DHCP Letter</td><td>☐External/Internal liaison (specify)</td></tr>
<tr><td>☐RMP update</td><td>☐Other (specify)</td></tr>
<tr><td colspan="2">Statement on validity/public health impact</td></tr>
<tr><td colspan="2">In light of the 2021 COVID-19 national vaccine rollout, there is likely to be a high public health impact.'</td></tr>
<tr><td colspan="2">Specific instructions for selected regulatory action(s)</td></tr>
<tr><td colspan="2">Nil</td></tr>
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References

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Medicines and Vaccines Investigation Section

Evaluation

Title	**Covid 19 Vaccines and Cerebrovascular Accident (CVA)/Stroke**
Date	**June 2022**
TRIM reference	**D22-5361616**

Issue summary

This issue originally arose following the detection of a potential signal of Vaxzevria vaccine and risk of cerebrovascular accident (CVA) in the TGA's routine disproportionality analysis (DPAR) using adverse event reporting data from March – June 2021. Consideration of the risk of CVA/stroke with Comirnaty vaccine arose following review of a self-controlled case series looking at the risk of thrombocytopenia and thromboembolic events associated with covid-19 vaccination in adults in England. [1]

As a result of the above signals, a Targeted Investigation Process (TIP) was completed by the Surveillance and Targeted Review Stream (STRS) of the Medicine and Vaccine Investigation Section (MaVIS) looking at the risk of CVA/stroke with both Vaxzevria (previously COVID-19 vaccine AstraZeneca) and Comirnaty. The targeted review concluded that more information was required and as a result both sponsors for Comirnaty (Pfizer) and Vaxzevria (AstraZeneca) were requested to provide their own analysis to the TGA of the issue.

In addition, the targeted review recommended that additional preferred terms (PT) be included in the Adverse Event of Special Interest (AESI) list for CNS haemorrhages and cerebrovascular accidents and that this be considered by the Vaccine Epidemiology Response and Assessment (VERA) team. [2]

Evaluation purpose

The purpose of this evaluation is to assess the evidence including the sponsor evaluations from AstraZeneca and Pfizer to determine if any regulatory action is required in relation to this issue. The other mRNA vaccine available in Australia, Spikevax (Moderna) will also be considered as part of this evaluation.

In addition, the specific risk of retinal vessel occlusion will be addressed with respect to Vaxzevria vaccine.

This evaluation will not include an analysis of cerebral venous sinus thrombosis (CVST) or other cerebral venous thromboses. Although these are classified as a type of stroke this issue has already been considered in a separate evaluation looking at Covid-19 vaccines and venous thromboembolism (VTE).

Product details

Vaxzevria

Vaxzevria has provisional approval for the indication:

Active immunisation of individuals ≥18 years old of the prevention of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2. [3]

Vaxzevria 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

Comirnaty has provisional approval for the indication:

Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 12 years of age and older. [4]

Comirnaty comprises a nucleoside-modified messenger RNA (mRNA) 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

Spikevax (elasomeran) COVID-19 vaccine has provisional approval for the indication:

Active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in individuals 6 years of age and older. [5]

Spikevax is an mRNA vaccine like Comirnaty.

Australian Technical Advisory Group on Immunisation (ATAGI) recommendations

ATAGI have made the following recommendations in relation to COVID-19 vaccination[6]:

- mRNA vaccines (eg Comirnaty or Spikevax) are preferred over Vaxzevria in people aged <60 years, and in pregnant people. Vaxzevria continues to be recommended in people aged 18 to <60 years when the benefits outweigh the risks, including in outbreak settings.
- For all individuals aged 16 years and above, a single booster dose of COVID-19 vaccine is recommended for those who completed their primary course, 3 or more months ago.
- Severely immunocompromised individuals are recommended to receive a third primary dose of COVID-19 vaccine to address the risk of suboptimal or non-response to the standard 2 dose schedule. An mRNA COVID-19 vaccine (Pfizer or Moderna) or the Novavax COVID-19 vaccine can be used for this third dose. Vaxzevria is not preferred for this third dose. Vaxzevria can be used for the third dose for individuals who have received Vaxzevria for their first 2 does if there are no contraindications or precautions for use, or if a significant adverse reaction has occurred after a previous mRNA vaccine dose which contraindicates further use of mRNA vaccine.
- Severely immunocompromised individuals aged 16 years and above who have received a third dose of a primary COVID-19 vaccine, are also recommended to receive a booster dose 3 months after the third primary dose, in line with the timing for the general population.
- Either of the available mRNA COVID-19 vaccines (Pfizer or Moderna) is preferred for this booster dose in those aged 18 years and above. For those aged 16-17 years, only Pfizer vaccine should be used.
- For people who have received a primary course of Vaxzevria vaccine, including those who are severely immunocompromised, Vaxzevria is no longer a recommended vaccine for use as a booster, even when there are no contraindications or precautions for its further use. However, it can still be used for this purpose in individuals who decline receiving and mRNA vaccine as a booster dose.
- The only scenario in which a booster dose using AstraZeneca is actively recommended is for people with medical contraindications to the Pfizer and/or Moderna vaccines.
- Nuvaxovid (Novovax) has been provisionally approved by the TGA for use in a primary course of COVID-19 vaccination. There are limited data on the safety and immunogenicity of Novavax as a booster dose and it is not TGA registered for that indication. ATAGI advises that Novanax can be used as a booster dose in an individual aged 18 or older if not other COVID-19 vaccine brand is suitable for that individual.
- An additional booster dose to increase vaccine protection before winter (winter dose) is also recommended for specified people at highest risk of severe COVID-19. The winter dose can be given from 4 months after the first booster dose.

Event description

Stroke or CVA is classified into two major types:

- Brain ischemia due to thrombosis, embolism or systemic hypoperfusion
- Brian haemorrhage due to intracerebral haemorrhage or subarachnoid haemorrhage (SAH)

A stroke is the acute neurological injury that occurs as a result of either of these pathologic processes. Approximately 80 percent of strokes are ischaemic, and 20 percent are haemorrhagic. In addition, when an embolus blocking a major vessel migrates, lyses or disperses within minutes to days, recirculation into the infarcted area can cause a haemorrhagic infarction and may aggravate oedema formation due to disruption of the blood-brain barrier.

Clinically, stoke symptoms and neurological deficits will be dependent on the anatomical territory affected by the ischaemia or haemorrhage.

A related condition, transient ischaemic attack (TIA) is defined clinically by the temporary nature of the associated neurological symptoms, which last less than 24 hours. It is now recognised that TIAs can also be associated with permanent brain tissue injury.

Another cause of stroke is occlusion of veins that drain blood away from the brain. Venous occlusion can result in fluid build up and brain oedema and in addition may cause brain ischaemia or haemorrhage. The focus of this evaluation will however by stroke due to arterial occlusion or cerebral haemorrhage. [7]

Retinal Vessel Occlusion

Occlusion of retinal vessels typically presents with acute persistent or transient visual loss. This can be due to occlusion either retinal arteries or veins. There are a number of other possible causes of such symptoms which will not be addressed in the context of this evaluation. Amaruosis fugax is a term used to describe transient visual loss.

As noted, retinal vessel occlusion can be either arterial or venous. Retinal artery occlusion is considered a form of stroke and presents with acute painless loss of monocular vision.

Retinal vein occlusion (RVO) is an important cause of visual loss among older adults throughout the world. RVO is the second most common cause of vision loss from retinal vascular disease, following diabetic retinopathy. Retinal vein occlusion is divided into branch retinal vein occlusion (BRVO), central retinal vein occlusion (CRVO) and hemi-retinal vein occlusion (HRVO). Patients may describe a scotoma or larger visual field deficit with blurred or grey vision corresponding to the area of occlusion which is usually painless. Patients may also experience premonitory symptoms such as scintillations. The visual field defect may develop over hours to weeks and commonly due to macular oedema. [8]

Reporting to AEMS s33

TGA Adverse Event Management System (AEMS)

A search of AEMS on 16 June 2022 was performed looking at ischaemic and haemorrhagic strokes using the Standard MedDRA Query (SMQ)

- Ischaemic central nervous system vascular conditions; and
- Haemorrhagic central nervous system vascular conditions.

The search strategy excluded cases of thrombosis with thrombocytopenia (TTS).

SMQ Ischaemic central nervous system vascular conditions

Comirnaty

There were a total of 325 cases from this SMQ reported with Comirnaty. Of these, the most commonly reported terms included:

- Cerebrovascular accident (188)
- Transient ischemic attack (72)
- Ischaemic stroke (14)
- Cerebral infarction (10)
- Retinal artery occlusion (6)
- Cerebral thrombosis (5)
- Embolic stroke (5)

Vaxzevria

There were a total of 552 cases from this SMQ reported with Vaxzevria. Of these, the most commonly reported terms included:

- Cerebrovascular accident (304)
- Transient ischaemic attack (113)
- Cerebral infarction (35)
- Ischaemic stroke (28)
- Retinal artery occlusion (11)
- Lacunar infarction (10)
- Cerebellar stroke (7)
- Cerebral artery thrombosis (7)
- Cerebral venous thrombosis (6)
- Cerebral thrombosis (5)

Spikevax

There were a total of 28 cases from this SMQ reported with Spikevax. Of these the following terms were reported:

- Cerebrovascular accident (14)
- Transient ischaemic attack (4)
- Cerebral thrombosis (2)
- Ischaemic stroke (2)
- Basal ganglia infarction (1)
- Cerebellar stroke (1)
- Cerebral infarction (1)
- Lacunar stroke (1)
- Spinal cord infarction (1)
- Thalamic infarction (1)

SMQ Haemorrhagic central nervous system vascular conditions

Comirnaty

There were a total of 245 cases from this SMQ reported with Comirnaty. Of these, the most commonly reported terms included:

- Cerebrovascular accident (188)
- Cerebral haemorrhage (20)
- Subarachnoid haemorrhage (11)
- Haemorrhage intracranial (7)
- Subdural haematoma (5)
- Basal ganglia haemorrhage (4)

The cases were fairly evenly divided between genders with slightly more cases in female patients (50.0%) than males. There were 56 cases in the age range 18-44, there were 77 cases in the age range 45 – 64, there were 30 cases in the age range 65-74 and 58 case in 75 and above age range. There were a further 3 cases reported in the children/adolescents.

Vaxzevria

There were a total of 407 cases from this SMQ reported with Vaxzevria. Of these, the most commonly reported terms included:

- Cerebrovascular accident (304)
- Cerebral haemorrhage (28)
- Haemorrhage intracranial (22)
- Subdural haematoma (17)
- Subarachnoid haemorrhage (15)
- Cerebellar stroke (7)
- Haemorrhagic stroke (7)
- Ruptured cerebral aneurysm (4)
- Subdural haemorrhage (4)

The cases were fairly evenly divided between genders with slightly more cases in male patients (50.9%) than females. In terms of the age range, 12 cases were reported in the 18-44 year age range, 86 cases were reported in the 45-64 year age range, 121 cases in the 65-74 age range and 174 cases in the 75 years and above age range.

Spikevax

There were a total of 17 cases from this SMQ reported with Spikevax. Of these the following terms were reported:

- Cerebrovascular accident (14)
- Cerebellar stroke (1)
- Cerebral haemorrhage (1)
- Haemorrhagic stroke (1)
- Subdural haematoma (1)

There was again a fairly even divide between genders despite small numbers in the Spikevax group. There were 2 cases reported in the 18-44 age range, there were 6 cases reported in the 45-64 age range, there were 5 cases in the 65-74 age range and 2 cases in the 75 and above age range.

There is some duplication of terms between these two SMQs, for example both include the most frequently reported term, cerebrovascular accident so this must be taken into consideration when comparing the two groups. It is also noted that more cases seem to appear in older age ranges for Vaxzevria than Comirnaty but this may reflect the ATAGI recommendations that Comirnaty is the preferred vaccine for people under 60 years.

Retinal vessel occlusion

A further search of AEMS was performed on 16 June 2022 for Vaxzevria specifically and the following terms relating to retinal vessel occlusion:

- Retinal artery embolism
- Retinal vascular disorder
- Retinal vein thrombosis
- Retinal artery occlusion
- Retinal vascular occlusion
- Subretinal haematoma
- Amaurosis fugax
- Retinal vascular thrombosis
- Retinal infarction
- Retinal ischaemia
- Retinal vein occlusion

There were 50 cases in total with the following results:

- Retinal vein occlusion (30)
- Retinal artery occlusion (11)
- Retinal vein thrombosis (5)
- Amaurosis fugax (2)
- Retinal artery embolism (2)
- Retinal vascular thrombosis (1)

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Australian PI and guidelines

There is no reference to stroke or CVA in the Australian PIs for Vaxzevria, Comirnaty or Spikevax.[3, 4, 5]

The PI for Vaxzevria has information in section 4.4 regarding coagulation disorders which include thrombosis and thrombocytopenia, venous thromboembolic events without thrombocytopenia and thrombocytopenia.

In particular, the Vaxzevria PI has the following information:

> *Thrombosis and thrombocytopenia*
>
> *A very rare and serious combination of thrombosis and thrombocytopenia including thrombosis with thrombocytopenia syndrome (TTS) in some cases associated with bleeding, has been observed following vaccination with Vaxzevria during post-marketing use. This includes cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia. The majority of events occurred withing the first 21 days following vaccination but have also been reported after this period. Some events had a fatal outcome. The reporting rates after the second dose are lower compared to after the first dose.*
>
> *…*
>
> *Venous thromboembolic events without thrombocytopenia*
>
> *Venous thromboembolic events without accompanying thrombocytopenia, including events of cerebrovascular venous and sinus thrombosis (CVST) have been reported following vaccination with Vaxzevria. Although a causal relationship has not been established, these events can be fatal and may require different treatment approaches than TTS. Healthcare professionals should consult applicable guidance.*

In addition, there is a section with information on neurological events however this does not include reference to stroke or CVA but rather warns about the risk of Guillain Barre Syndrome (GBS), transverse myelitis and other rare demyelinating conditions. [3]

Overseas labelling

Vaxzevria

There is no reference to stroke or CVA in the labelling for this product in Canada, the EU or New Zealand. These documents are broadly consistent with the information contained in the Australian PI with some minor variations.

Vaxzevria is not registered for use in the US.

Comirnaty

There is no reference to stroke or CVA in the labelling for this product in Canada, the EU, the US or New Zealand.

Spikevax

There is no reference to stroke or CVA in the labelling for this product in Canada, EU or the US. Spikevax is not registered for use in New Zealand.

Sponsor's reports

Both AstraZeneca and Pfizer were requested to provide analyses of this issue to the TGA. Both sponsors were requested to provide an analysis of the company held data on CVA/stroke including (but not limited to) the following:

- An observed versus expected analysis:
  - Stratified by age and gender
  - Including risk windows out to 7, 14, 21 and 42 days
  - Excluding cases of thrombosis with thrombocytopenia syndrome (TTS)
- Discussion regarding the preferred terms included and excluded from the background rates utilised for analysis should be provided (list of recommended PTs provided)
- An analysis of any global company held safety data, case reports and literature regarding the risk in question and COVID-19 vaccines.
  In addition to the results and analysis of these searches, please include:
  - The literature search strategy
  - The MedDRA search terms used to identify global case reports and rationale for selection of these (see list of recommended search terms)
  - The case series inclusion and exclusion criteria, with justification for these
- A discussion of the biological plausibility for the association between the risk in question and COVID-19 vaccines.
- Details of any overseas regulatory actions undertaken relevant to the signal.

The following terms were provided to the AstraZeneca and Pfizer for reference. These terms were identified from the MedDRA SMQs 'haemorrhagic central nervous system vascular conditions' and 'ischaemic central nervous system vascular conditions.'

Recommended search terms for cerebrovascular accident/stroke

amaurosis fugax	cerebral haematoma	intraventricular haemorrhage
basal ganglia haemorrhage	cerebral haemorrhage	ischaemic stroke
basal ganglia stroke	cerebral infarction	lacunar infarction
basal ganglia stroke	cerebral ischaemia	retinal artery occlusion
basilar artery occlusion	cerebral small vessel ischaemic disease	ruptured cerebral aneurysm
brain hypoxia	cerebral thrombosis	subarachnoid haemorrhage

brain stem haemorrhage	cerebral venous thrombosis	subdural haematoma
brain stem infarction	cerebrovascular accident	subdural haemorrhage
brain stem stroke	cerebrovascular disorder.	thalamic infarction
carotid artery occlusion	embolic stroke	thalamus haemorrhage
carotid artery thrombosis	extradural haematoma evacuation	transient ischaemic attack
cerebellar artery thrombosis	extradural haematoma	vertebral artery occlusion
cerebellar haemorrhage	haemorrhage intracranial	vertebrobasilar insufficiency
cerebellar infarction	haemorrhagic cerebral infarction	vertebrobasilar stroke.
cerebellar stroke	haemorrhagic stroke	
cerebral artery thrombosis	haemorrhagic transformation stroke	

In addition, AstraZeneca were requested to provide an additional analysis looking specifically at retinal vessel occlusion with the following preferred terms:

Retinal artery embolism	Retinal vascular disorder	Retinal vein thrombosis
Retinal artery occlusion	Retinal vascular occlusion	Subretinal haematoma
Retinal infarction	Retinal vascular thrombosis	Amaurosis fugax
Retinal ischaemia	Retinal vein occlusion	

1. **Comirnaty (Pfizer)**

Pfizer provided their analysis of the signal to the TGA on 10 March 2022. In their report they stated that the safety database was searched for all Pfizer-BioNTech COVID-19 vaccine adverse event reports cumulatively through to 18 December 2021 that contained the 45 PTs recommended by the TGA.

A total of 8934 cases were retrieved, some cases reported multiple PTs. There were a total of 1072 fatal cases. There were 4719 females and 4024 males and gender not reported in 191 cases. The mean and median ages were 69.9 and 70 years respectively.

Out of the 8934 cases, 6858 cases were reported between day 0 and day 42 post vaccination. The sponsor noted that a wide time range was chosen as a plausible mechanism of action was unknown. They then provided an analysis by age range.

The sponsor performed a literature search and identified 10 relevant publications including the article by Hipsley-Cox et al that triggered evaluation of this issue with respect to Comirnaty. They summarised the findings of each article and noted that out of the 10 studies, 2 reported a correlative association between BNT162b2 vaccine and ischaemic or haemorrhagic stroke. Seven studies did not support an association between BNT162b2 vaccine and haemorrhagic or ischaemic stroke and in the remaining publication by Patone et al an increased risk of haemorrhagic stroke after BNT162b2 vaccination was reported in a study in England but was not replicated in a Scottish study that was somewhat smaller. The sponsor concluded that overall the literature did not support a causal association between BNT162b2 and stroke and that further a plausible mechanism for how the vaccine could increase the risk of haemorrhagic or ischaemic stroke was not provided.

An observed versus expected analysis was also performed for cases reported to 18 December 2021 with 7, 14, 21 and 42 day risk windows. These were further stratified by age and gender for US and EEA countries because these countries make detailed information about vaccine administration publicly available. The

background rates were derived using the 2017-2019 ACCESS project data. The ACCESS sources for haemorrhagic and ischaemic stroke incidence rates were the Spanish Information System for the Development of Research in Primary Care (SIDIAP) and the Italian Regional Health Agency (ARS) databases, respectively. Based on these background rates the sponsor reported that all observed versus expected ratios for all stratifications were below 1, suggesting that the number of reported cases was not higher than expected compared to unvaccinated persons.

The sponsor noted several limitations to observed versus expected analyses for signal detection. They noted that the observed cases are likely to be underestimated due to underreporting that occurs with spontaneous report surveillance and that additional factors such as incomplete reporting and lags in reporting would also affect this. They further noted that spontaneous surveillance systems are prone to reporting bias whereby events that have been previously identified as potentially related to vaccine use are more likely to be reported even if they do not meet the clinical definition and conversely events that have not been previously associated with a vaccine are more likely to be underreported due to lack of recognition of a potential association.

The sponsor went on to say that some cases were missing information such as age, gender and/or time to onset. Time to onset was imputed for cases with missing values based on cases with known time to onset. Cases were then grouped by age and sex; those with unknown values were proportionally allocated across groups based on the known distributions of the characteristics.

Further limitations of the analysis were noted in that the exposure estimate assumes the number of reported vaccine administrations is complete and accurate when in fact not all countries have reported to the data source, therefore they concluded the exposure is underestimated. The expected count also assumes that the incidence rate in the vaccinated population is the same as that in the population used to calculate the background rate. It is also possible that the populations used in the background rate (from Spain and Italy) differ from those expected in the vaccinated population.

The sponsor summarised their findings and noted that there are known risk factors for ischaemic and haemorrhagic strokes associated with age and cardiovascular morbidity. Further, that infection from COVID-19 itself has been associated with thromboembolism. They noted that 8934 cases were retrieved from the global database and as would be expected with the known epidemiology of stroke the number of reported cases was highest in the oldest individuals and proportionally decreased with age. The number of ischaemic strokes were higher than that of haemorrhagic strokes. The observed versus expected analyses did not support a higher than expected reporting of either type of stroke following vaccination and the medical literature did not uniformly support a correlation between stroke and vaccination with Comirnaty vaccine. The minority of publications that did find a correlation reported only mildly elevated incidence rate ratios. No regulatory action has been taken relevant to this signal. Considering all of this, Pfizer therefore concluded that the currently available evidence did not support a causal association between Comirnaty and ischaemic/haemorrhagic stroke and consequently no updates to labelling or risk management plans would be undertaken however they would continue to monitor this issue. [9]

2. Vaxzevria (AstraZeneca)

AstraZeneca provided their analysis of the issue to the TGA on 10 March 2022. Based on their assessment of clinical trial data, data from their global safety database, literature and observed versus expected analyses they concluded that there was insufficient evidence to suggest a causal association between Vaxzevria and CVA and that no updates to the product labelling were required currently. AstraZeneca also performed an evaluation of the risk of retinal arterial and venous thrombosis and found that no causal relationship had been established.

Clinical trial data

AstraZeneca searched their clinical trial database for adverse event reports of CVA from clinical studies (data cut-off date of 7 December 2020 for the Oxford pooled studies COV001, COV002, COV003 and

COV005 and 5 March 2021 for the US study D8110C00001). The PTs provided by the TGA were used for this search.

In the Oxford pooled studies there was one case (<0.1%) of CVA/stroke each in the treatment (N=12282) and control (N=11962) groups within 28 days of vaccination. Looking at the period from day zero to day 364 there were 2 cases in the treatment group and 7 in the control group.

In the US study, which has a 2:1 randomisation ratio, there were 8 cases of CVA/stroke in the treatment group (N=21587) (<0.1%) and 1 case in the placebo group (N=10792) (<0.1%) within 28 days after vaccination (any dose). Looking at the period from day zero to day 730 there were 8 cases (<0.1%) in the treatment group and 2 cases (<0.1%) in the placebo group.

The sponsor reported that overall the frequency of events was similar in both Oxford pooled studies and the US study, with relatively low numbers of events reported across the treatment arms.

Global patient safety database

A cumulative search of the AstraZeneca Global Patient Safety Database (cut-off 31 January 2022) was performed using the PTs recommended by the TGA. A total of 6299 cases were found. After excluding cases of TTS (284) and CVST (521) a total of 5494 cases were included in the analysis.

Of the 5494 cases, 48.8% were females and 48.4% were males with gender not reported in 2.7% of cases. The median age was 44.5 years, with 47.9% of cases falling between the ages of 18 and 65 years and 42.5% being ≥ 65 years with the most cases reported in the 60-69 age range (1433 cases, 26.1%). The majority of cases were from the UK (2311 cases, 42.1%) with cases from other countries being less than 10%. There were 504 cases reported from Australia (9.2%).

The most commonly reported PTs were cerebrovascular accident (2435 cases, 40.6%), transient ischaemic attack (1012 cases, 16.9%) and ischaemic stroke (613 cases, 10.2%). Of the 5494 cases the time to onset (TTO) was reported in 72.3% of cases and ranged from the day of vaccination to 461 days with a median TTO of 102 days.

The sponsor reported that 3614 cases (65.8%) were not medically confirmed and 1880 (34.2% were medically confirmed).

The sponsor provided a summary of 4 cases found published in the literature. The cases included 3 cases of ischaemic stroke and one of haemorrhagic stroke following immunisation with Vaxzevria. In all 3 cases the sponsor concluded that there was either missing information or confounding factors leading to the events.

The sponsor concluded that review of all cases revealed either multiple confounders for CVA such as medical history, concurrent medical conditions, social history, concomitant medications and risk factors) or insufficient information which precluded a proper assessment of the reports. As such they stated that no safety signal was identified.

Literature search

The sponsor conducted a literature search using a range of stroke terms and did an additional search to identify any relevant articles that discussed a possible mechanism by which Vaxzevria could be associated with CVA or stroke. Articles that related to CVA in the context of TTS or CVST were excluded. The sponsor identified 3 relevant articles (out of 92).

These included a study looking at spontaneous reports of adverse drug reactions reported to the regional pharmacovigilance unit in Portugal of which the most frequently reported important medical events included ischaemic stroke (for Comirnaty, Vaxzevira and Moderna). The sponsor noted a lack of case specific information which prevented a proper assessment of cause and effect relationships and Vaxzevria.

Another study evaluated the frequency of severe adverse events documented in the EudraVigilance European database in young and older adult (>65 years old) vaccine recipients and related them to coagulation disorders and arterial, cardiac, and nervous system events. The study reported that the

recipients of AstraZeneca/Janssen vaccine had higher frequencies of venous blood clots and haemorrhage, but also thromboembolic disease and arterial events including myocardial infarction and stroke compared to Pfizer/BioNTech both in young and older adults. The authors further found that AstraZeneca vaccine was associated with higher frequencies of severe adverse events in young adults and Janssen vaccine was associated with higher frequencies of severe adverse events in older adults. The sponsor again noted that a lack of case specific information prevented a proper assessment of cause and effect relationships and Vaxzevria.

A population based study (case control study) of over 32 million people investigated neurological complications associated with Covid 19 vaccines as well as Covid 19 infection. This study found an increased risk of haemorrhagic stroke with BNT162b2 but no increased risk of ischaemic or haemorrhagic stroke with Vaxzevria.

The sponsor also identified a study relating to the mechanism of action of CVA/stroke as an adverse event but considered there to be insufficient information on the etiopathogenesis of CVA or confounders were identified CVA.

Observed versus expected analysis

The sponsor conducted an observed versus expected analysis. All cases were stratified by risk windows of 28 and 42 days including and excluding cases with unknown time to onset. Stratification by age was performed for case reports from the European Economic Area (EEA) and stratification by age and gender was performed for cases from the UK. The chosen risk windows were used to align with other thrombosis concepts that Astra Zeneca had previously analysed, and they further stated that 42 days was chosen conservatively as the majority of cases fell within that risk window.

The analysis was divided into two groups, one looking at CVA excluding TIA and another looking at CVA involving TIA. The CVA excluding TIA group included observed versus expected analysis for all stroke including with unknown TTO and further categorised analyses for intracerebral haemorrhage, ischaemic stroke excluding TIA and subarachnoid haemorrhage. The analysis was then stratified for all stroke cases by gender and age group as described above.

Background rates for stroke were determined from a publication by Akyea et al and for TIA from Rothwell et al. The sponsor provided an explanatory statement for the choice of background rate for stroke (Akyea et al) but not for TIA background rates.

For all stroke events excluding TIA with known TTO the observed number of cases were either less than or significantly less than expected.

When cases with unknown TTOs were included in the analysis the observed number of cases were significantly greater than expected in females in the UK within the 20 -29 and 30-39 aged groups with a 28-day risk window. The observed number of cases were greater than expected in females in the UK within the 20-29 and 30-39 age groups with a 42-day risk window, and in in males in the UK within the 20-29 age group with 28-day and 42-day risk windows.

The sponsor noted that most of the cases reported from the UK did not have sufficient information to do a causality assessment.

For the TIA cases, the observed number of cases were significantly less than or less than expected across all stratifications.

In their discussion, the sponsor reviewed the sources of information included in the report. They noted that in the clinical trial data although there was a numerical imbalance in the US study, the number of events occurring across the treatment arms were low. In their review of the post-market cases they did not identify a signal or index case and they commented that the majority of cases in their database were not medically confirmed. Their analysis of the available literature did not identify any publications describing a causal association between CVA and Vaxzevria. In their view the observed versus expected analysis indicated that the observed cases were less than or significantly less than the expected for global data and

for all age and gender stratifications. They therefore considered that there was insufficient evidence to suggest a causal association between Vaxzevria and CVA and that no update to the product information was warranted at this time. They further noted that AstraZeneca would continue to monitor case reports of CVA during safety surveillance activities for Vaxzevria and take further actions as deemed necessary.

Retinal Vessel Occlusion

The sponsor addressed the issue of the risk of retinal vessel occlusion by stating that they had performed a comprehensive evaluation of the issue and that their opinion was that a reasonable possibility of a causal relationship between Vaxzevria and retinal vessel occlusion had not been established. [10]

TGA Analysis

Analysis performed by the TGA Vaccine Epidemiology Response and Assessment (VERA) team did not show reporting of ischaemic or haemorrhagic stroke at rates higher than expected. An observed versus expected analysis did not flag a signal for either ischaemic or haemorrhagic stroke for any of the vaccines (Vaxzevria, Comirnaty or Spikevax) using the same terms provided to the sponsors for their analysis from 6 June 2021 to 17 January 2022. [11, 12]

Literature

The article that prompted investigation of CVA/stroke with Comirnaty was a self-controlled case study looking at the risk of thrombocytopenia and thromboembolism after covid-19 vaccination. The study evaluated the short term risks of thrombocytopenia, venous thromboembolism and arterial thromboembolism associated with the first dose of the ChAdOx1 nCoV-19 and BNT162b2 vaccines, or a SARS-CoV-2 positive test in England between 1 December 2020 and 24 April 2021. They also evaluated the risk of prespecified secondary outcomes of interest, namely CVST, ischaemic stroke, myocardial infarction and other rare arterial thrombotic events according to a prespecified protocol.

This study found an increased risk of thrombocytopenia, venous thromboembolism and other rare arterial thrombotic events after the first dose of the ChAdOx1 nCoV-19 vaccine and an increased risk of arterial thromboembolism and ischaemic stroke after the first dose of the BNT162b2 (Pfizer) vaccine. The authors did note that the risks of these events were much lower than those associated with SARS-CoV-2 infection in the same population. [1]

A literature search on 20 June 2022 for “covid-19 vaccines” and “cerebrovascular accident” was conducted to identify any further literature articles since Pfizer and AstraZeneca completed their respective reports. Seven relevant publications were identified with 3 of these consisting of case reports.

A retrospective cohort study from Argentina looked at 29 985 patients vaccinated with either AstraZeneca, Sputnik or Sinopharm with primary end point of a symptomatic thrombotic event (deep vein thrombosis, pulmonary embolism, acute ischaemic stroke, acute coronary syndrome or arterial thrombosis). An historic control group was used of patients vaccinated with influenza vaccine between January and May 2019. The authors found a significant increase in reporting of thrombotic events in patients vaccinate with a covid 19 vaccine compared to influenza vaccine. Regarding the independent outcomes no significant differences were found in the thrombotic event categories, except cumulative incidence of acute coronary syndrome which was higher in the covid 19 vaccine group. The comparison between the adenovirus vector platform-based vaccine and the inactivated virus vaccine did not demonstrate significant differences. [13]

A systematic review of thromboembolic events in 286 patients looked at thromboembolic events (both venous and arterial) following covid 19 vaccination. Twenty studies were included in the analysis and the majority of these involved the AstraZeneca vaccine with a greater proportion of the studied population being female (67.4%). The review found that venous thrombosis (74.8%) was more common than arterial thrombosis (27.9%), and in patients experiencing arterial thrombosis, myocardial infarction was the most common manifestation of this followed by stroke. Cerebral sinus thrombosis was the most common manifestation (28.3%) of venous thrombosis followed by deep vein thrombosis. The majority of patients

had a thrombocytopenia (49%) and antiplatelet factor 4 antibodies (78.6%). Overall thromboembolic events were most commonly reported following vaccination with the AstraZeneca vaccine. [14]

A case control study from Italy looked at patients admitted to hospital from 1 February 2021 to 31 July 2021 with ischaemic stroke within 4 weeks of covid 19 vaccination and compared their main features with those of all other patients with ischaemic strokes admitted during the same period. The authors reported that ischaemic strokes occurring shortly after covid 19 vaccination were similar to those of non-vaccinated patients and hypothesised that the relatively high percentage of such patients probably related to the very high fraction of elderly people vaccinated against covid-19 rather than to a consequence of vaccination.[15]

Another study looking at stroke among covid 19 vaccine recipients in Mexico analysed the stroke incidence per million doses among hospitalised adult patients during an 8 month period. Adverse events following immunisation (AEFIs) were defined as clinical events occurring within 30 days of immunisation. Acute ischaemic stroke, intracerebral haemorrhage, subarachnoid haemorrhage and cerebral venous thrombosis cases were collected through a passive epidemiologic surveillance system. Six different vaccines were involved in this analysis including BNT162b2 and ChAdOx1 nCov-19. The authors found 56 patients with acute stroke (43 with acute ischaemic stroke, 9 with intracerebral haemorrhage, 2 with subarachnoid haemorrhage and 2 with cerebral venous thrombosis) suggesting that stroke was a rare event. In addition, most patients had underlying stroke aetiology and leaving only a temporal association with vaccination. They authors concluded that stroke was a very rare AEFI and following a discussion of the limitations of the data stated that the results could not be used to determine causation and further research was required. [16]

There were also a number of case reports in the literature. [17, 18, 19]

A further search for “chadox1” and “retinal” and “Vaxzevria” and “retinal” returned relevant publications which mainly consisted of case reports.

A study to assess vascular retinal findings temporally related to covid 19 vaccination from Brazil looked at 11 patients that developed visual complaints after covid 19 vaccination. Of the 11 patients, 5 had arterial occlusion, 4 had venous occlusion and 2 had nonspecific vascular alterations suggestive of retinal ischaemia. The authors noted that in each case there was a temporal association with vaccination and while could not attribute causality, emphasised the need to continue to observe such events with robust epidemiological surveys to better elucidate causality. [20]

As noted above a number of case reports were also identified. [21, 22, 23, 24]

Discussion

Stroke or CVA, either ischaemic or haemorrhagic are serious life-threatening conditions that carry significant morbidity and disability. Unfortunately, stroke is common and is associated with a number of risk factors including advancing age, hypertension, smoking, obesity, diabetes and family history. Increased risk of stroke has also been associated with Covid-19 infection.

Sponsor reports

The reports submitted by each of the sponsors is summarised above. Observed versus expected analysis were performed by but each approached the analysis differently. Pfizer provided 3 risk windows as requested by the TGA however AstraZeneca provided only 2, however justified this by stating that this was consistent with other analysis they had performed on similar issues.

While Pfizer divided their observed versus expected analysis into two groups – haemorrhagic stroke cases and ischaemic stroke cases, AstraZeneca used a different approach by dividing the analysis into CVA excluding TIA and CVA involving TIA. Each sponsor also used different background rates in their analyses which may contribute to differences in overall findings.

Pfizer did not find higher rates of observed cases compared to those expected in any of the stratifications and this combined with their other analysis including a literature search, including the article by Hippisley-Cox et al, formed the basis of their conclusion that there was insufficient evidence to support a causal association at this time.

AstraZeneca similarly came to the conclusion that there was insufficient evidence to suggest a causal association between their vaccine and CVA. In their observed versus expected analysis the sponsor found that for all stroke events excluding TIA with known TTO the observed number of cases were either less than or significantly less than expected. When they repeated the analysis and included cases with unknown time to onset some age stratifications, notably in younger age brackets, were greater than expected. When the sponsor looked at CVA cases involving TIA the observed number of cases were significantly less than or less than expected across all stratifications.

AstraZeneca was asked to provide a separate analysis of retinal vessel occlusion with specified search terms however did not provide a separate observed versus expected analysis for these cases nor expand on any details of their analysis of this issue other than stating that they had performed a comprehensive evaluation of retinal artery/venous occlusion and found that no reasonable possibility of a causal relationship had been established.

Turning to other aspects of this evaluation, at this time no regulatory action has been taken by other major international regulators in respect of this issue and the Australian labelling is consistent with that in the UK, US and Europe.

The TGA has many reports of stroke following Covid-19 vaccination as detailed above however note that the analysis performed by the VERA team did not show reporting of ischaemic or haemorrhagic stroke at rates higher than expected for either vaccine.

s33

There have been studies in the literature discussed above that have identified higher rates of stroke associated with covid 19 vaccination, in particular the study by Hippisley-Cox et al [1] however this alone may not be sufficient to support regulatory action at this time when looked at together with the evidence discussed in this evaluation as a whole.

Conclusion and recommendations

Taking into account information presented above as a whole, and the reports provided by the sponsors it is recommended that no regulatory action be required currently however this issue continue to be subject to routine monitoring. This supported by reassuring observed versus expected analysis by the sponsors and also an earlier TGA analysis, as well as a lack of international regulatory action.

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