NOT FOR PUBLICATION

COMMISSION ON HUMAN MEDICINES

VACCINE BENEFIT RISK EXPERT WORKING GROUP

Title of paper: COVID-19 Vaccines and risk of thromboembolic events with concurrent thrombocytopenia

Type of paper: For advice

Active(s) rINN	AstraZeneca COVID-19 vaccine Pfizer/BioNTech COVID-19 vaccine BNT162b2 Moderna COVID-19 vaccine BNT162b2
Product name(s)	
Marketing Authorisation Holder(s)	AstraZeneca Pfizer/BioNTech Moderna
Legal status	Prescription only medicines
Therapeutic classification **(ATC code)**	
Previous assessments	
Assessor(s)	Name: [redacted] (Scientific Assessor) Email: [redacted] Name: [redacted] (Senior Medical Assessor) Email: [redacted] Name: Dr Katherine Donegan (Pharmacoepidemiology assessor) Email: katherine.donegan@mhra.gov.uk Name: [redacted] (Scientific Assessor) Email: [redacted]

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1. Introduction

The Pfizer/BioNTech COVID-19 vaccine was authorised for use under Regulation 174 by the MHRA on 2 December 2020. It is estimated that over 11 million doses have been administered in the UK as of 8 March 2021. The AstraZeneca COVID-19 vaccine was authorised for use under Regulation 174 by the MHRA on 30 December 2020, and over 11 million doses have been administered in the UK as of 7 March 2021. More recent data from PHE (as of 15 March) which is not brand specific indicates in total over 24 million doses have been administered[1].

Over the last week, the Austrian National Competent Authority and the Danish Health and Medicines Authority suspended use of COVID-19 vaccine AstraZeneca as a precautionary move following reports of events of thromboembolic events occurring with use of the vaccine. This has since been followed by suspension in multiple other countries, mostly in the EU, including Ireland, Norway, Iceland, Austria, Estonia, Lithuania, Luxembourg, Italy, Latvia, and most recently, France, Spainand Germany. Although the signal originally appeared to concern thromboembolic events more generally, it was since reported a cluster of three [redacted] cases from [redacted] reporting apparent immune thrombocytopenia in conjunction with cerebral venous sinus thromboses in young individuals (aged [redacted] within 7 to 10 days of vaccination. This was reported along with patient reports of bruising suggestive of thrombocytopenic events and a case of portal venous thrombosis in an individual without apparent thrombocytopenia. These cases from [redacted] which prompted the action Ireland, are provided in Annex 1. The Paul Ehrlich Institute subsequently issued a statement on the 15th of March specifically noting cases of cerebral venous sinus thrombosis and thrombocytopenia. PEI stated the following:

> "After intensive consultations on the serious thrombotic events that have occurred in Germany and Europe, the Paul Ehrlich Institute recommends the temporary suspension of vaccinations with the COVID-19 vaccine AstraZeneca.
>
> Compared to the status of March 11th, 2021, further cases (status: Monday, March 15th, 2021) have been reported in Germany. When analyzing the new data, the experts at the Paul Ehrlich Institute now see a noticeable increase in a special form of very rare cerebral vein thrombosis (sinus vein thrombosis) in connection with a lack of blood platelets (thrombocytopenia) and bleeding close to vaccinations with the COVID-19 vaccine AstraZeneca.
>
> The data will be further analyzed and assessed by the European Medicines Agency (EMA).
>
> Until the evaluation by the EMA has been completed, vaccinations with the COVID-19 vaccine from AstraZeneca in Germany will be suspended. Today's decision concerns both initial and follow-up vaccinations.
>
> The Paul Ehrlich Institute would like to point out that people who have received the COVID-19 vaccine AstraZeneca and feel increasingly unwell more than four days after the vaccination - e.g. with severe and persistent headaches or punctiform skin bleeding – should seek medical attention immediately ".

According to further information posted by Science Media Centre, it is understood that the PEI action was prompted by 7 case reports following 1.6 million doses in Germany, and that this type of thrombosis occurs in the general population about two to five times per million people per year

[1] Vaccinations | Coronavirus in the UK (data.gov.uk)

[Devasagayam S et al. (2016): Cerebral Venous Sinus Thrombosis Incidence Is Higher Than Previously Thought. A Retrospective Population-Based Study. Stroke; 47 (9): 2180–2182. DOI: 10.1161/STROKEAHA.116.013617.]. Individual cases of sinus vein thrombosis have also been described with COVID disease [Abouhashem S et al. (2021): Cerebral venous sinus thrombosis in patients with COVID-19 infection . Interdisciplinary Neurosurgery; 24. DOI: 10.1016/j.inat.2021.101091. And Dakay K t al. (2021): Cerebral Venous Sinus Thrombosis in COVID-19 Infection: A Case Series and Review of The Literature. J Stroke Cerebrovasc Dis; 30 (1):105434. DOI: 10.1016/j.jstrokecerebrovasdis.2020.105434.]

The EMA's safety committee PRAC is urgently reviewing the issue of thromboembolic events this week, including events of thrombosis occurring with concurrent thrombocytopenia. The EMA has issued several communications around the review, the most recent of which was circulated on 15 March 2021, and is provided in Annex 7. The EMA communications highlight the preliminary view suggests benefit risk of the AstraZeneca vaccine remains positive, and that the suspensions have been taken as a precautionary measure.

The UK review is presented below; this focuses on UK specific data on venous thromboembolic events occurring more generally along with an evaluation of cases of thrombocytopenia, with and without venous thromboembolic events. Of note, the review of the risk of immune thrombocytopenia with COVID-19 vaccines was recently discussed at the EWG on the 25th of February.

Cerebral venous sinus thrombosis, thrombocytopenia and paradoxical thrombosis

Cerebral venous sinus thrombosis is a rare form of venous thrombosis, occurring at an estimated annual incidence in adults of around 5 per million people[1]. Recently, a cross-sectional study in the Netherlands and a population-based study in Australia, found a much higher incidence of up to 1.6 per 100,000 per year 12, 13.

It is itself multifactorial, with a higher incidence amongst females, and diagnosis can be challenging due to presentation with a wide spectrum of clinical events. Clinical manifestations can vary from acute (less than 48 hours) to subacute (48 hours to 30 days). Symptoms most commonly include headache but can otherwise be diverse including focal neurological signs, headache, changes in mental state and symptoms of raised intracranial pressure[2]. Risk factors are associated with a multitude of acquired and inherited events, these include other central nervous system events such as intracranial neoplasias and infection, procedural events such as surgery and lumbar puncture as well as other systemic risk factors for thrombotic events eg: nephrotic syndrome, vasculitis, oral contraception and pregnancy[2]. In more than 85% of adult patients, at least 1 risk factor for cerebral venous thrombosis can be identified, most often a prothrombotic condition[3].

Cerebral venous sinus thrombosis, along with other paradoxical thromboembolic events, have been known to rarely occur in other immune thrombocytopenic states such as immune thrombocytopenia (ITP)[4,5] and heparin-induced thrombocytopenic thrombotic syndrome (HITT). Plausible mechanisms for the clinical paradox associating immune thrombocytopenia particularly with venous thromboembolic events have been postulated, including increased platelet microparticle thrombogenicity following peripheral destruction, increased antiphospholipid antibody activity[5] and increased levels of von Willebrand factor antigen[6].

Type 2 HITT is the more serious of the two types of HITT. It is a rare condition occurring in approximately 1- 3% of patients receiving heparin[7]. Events manifest secondary to an immunological

response leading to thrombocytopenia, bleeding and thrombosis. The time to onset is typically 4-10 days following heparin therapy. Clinical events occur secondary to an immune response to PF4/heparin, although the immune response is recognised to occur more frequently than clinical manifestations of thrombocytopenia or thrombosis[7]. Patients can experience thrombocytopenia concurrent with thrombosis, with thrombosis being the more severe complication and can be life-threatening[7]. Thrombotic events primarily affect the venous system, although arterial involvement can also occur[8].

Thrombotic thrombocytopenic purpura (TTP) presents with thrombocytopenia along with microvascular thrombosis and haemolytic anaemia with characteristic red cell fragments on peripheral smear[9]. Secondary forms can result from extrinsic triggers including autoimmune disorders, pregnancy and viral infection. This arises from antibodies to ADAMTS13, a protease that cleaves von Willebrand factor (VWF) multimers into smaller ones. This protease's deficiency leads to VWF giant multimers that bind to platelets, and coagulation factors promote the coagulation cascade.

Thrombocytopenia and thrombosis have also been associated with COVID-19 disease. The incidence of thrombocytopenia in patients with COVID-19 has been variable across studies. Mild thrombocytopenia has been observed in up to one-third of these patients, with even higher rate in patients with severe disease (57.7%) compared with non-severe disease (31.6%). ITP has also been known to occur with onset occurring in 20% of cases 3 weeks after onset of COVID-19 symptoms, with reports occurring after clinical recovery[11]. Cases of TTP have also been reported to occur[11]. The proposed mechanisms of thrombocytopenia with COVID-19 involve inhibition of platelet synthesis due to direct infection of the bone marrow cells or platelets by the virus (possibly via CD-13 receptors) and dysfunctional marrow microenvironment; virus-mediated liver damage leading to decreased thrombopoietin production; pulmonary endothelial damage followed by platelet aggregation in the lungs, subsequent formation of microthrombi, and platelet consumption; and finally, the destruction of platelets by the immune system.

1. Handley et al Health Information Management Journal 2020, Vol. 49(1) 58–61

2. Alvis- Miranda J Neurosci Rural Pract. 2013 Oct-Dec; 4(4): 427–438. doi: 10.4103/0976-3147.120236
3. Boulware R, Refaai MA. Thromb Res. 2020 Mar; 187:154–8
4. Hernandez et al, 2015 ACTA MEDICA PHILIPPINA 67, VOL. 49 NO. 1 2015
5. Sarpatwari A, Bennett D, Logie, JW, et al. Haematologica. 2010; 95(7):1167-75.
6. Rasheed et al, 2020 Case Rep Oncol 2020;13:588–594
7. Arepally, G, CLINICAL PLATELET DISORDERS| MAY 25, 2017
8. Majeed, T, 2010, Asian J Transfus Sci. 2010 Jul; 4(2): 137. doi: 10.4103/0973-6247.67028
9. Louw et al Thrombosis J 16, 35 (2018). https://doi.org/10.1186/s12959-018-0189-x
10. Tehrani et al, 2021 International Immunopharmacology 93
11. Bhatarcharjee 2020 SN Comprehensive Clinical Medicine https://doi.org/10.1007/s42399-020-00521-8
12. Coutinho Jet al Stroke. 2012;43:3375-3377.
13. Devasagayam S, et al Stroke. 2016;47:2180-2182.

2. Overall review of venous thromboembolic events

Pfizer/BioNTech COVID-19 vaccine and venous thromboembolic events

Yellow Card Data

The MHRA has received a total of **74 reports** relating to venous thromboembolic events of interest. The PTs reported in these cases and a summary of the details of these cases are provided below. One fatal case of pulmonary embolism also reports haematemesis alongside severe diarrhoea and vomiting; there are no other cases reporting bleeding events and no cases which also report thrombocytopenia or related events.

Reaction (PT)	No. of events reported
Cerebral venous sinus thrombosis	2
Pulmonary Embolism	34
Deep vein thrombosis	16
Thrombosis	18
Thrombophlebitis	5
Superficial thrombophlebitis	1
Pelvic venous thrombosis	1
Venous thrombosis	1
Pulmonary thrombosis	1
Pulmonary infarct	1
Cerebellar stroke	1
Embolic stroke	1
Vena cava thrombosis	1
Vena cava embolism	1

N.B. more than one PT can be reported in each case

Gender		Age		Time to onset	
Female	41	20-39 years	11	0-6 days	40
Male	30	40-59 years	21	7-14 days	14
Not reported	3	60-79 years	19	>14 days	13

	80+ years	14	Not reported
	Not reported	2	

Two of these cases are fatal:

- [redacted] *Assessor comment*: this case potentially represents bleeding events (haematemesis) with a thromboembolic event, however the haematemesis is likely secondary to the severe vomiting. Concurrent COVID-19 infection may also be a confounding factor, although this was asymptomatic.
- [redacted] *Assessor comment*: There are no specific details provided on the thrombosis reported and it is difficult to determine whether the MI was caused by a thrombotic event. Details of the other two cases are sought.

Considering the interest in AstraZeneca cases of cerebral venous sinus thrombosis, details of the two cases with Pfizer/BioNTech are provided here, however, neither of these cases report thrombocytopenia.

- [redacted]

Overall, 7 of these cases report events following the second dose of the vaccine, 29 of the cases reporting possible confounding factors for the thromboembolic events, and six of the cases report COVID-19 in close temporal association with the suspected adverse reactions.

Further summary details of these cases can be found in annex 5.

Company review of thromboembolic events

Pfizer/BioNTech have reviewed thromboembolic events in the most recent Summary Monthly Safety report as part of the adverse events of special interest under continual review, and the search covered the following terms: *Embolism and thrombosis (HLGT) (Primary Path), excluding PTs reviewed as Stroke AESIs, OR PTs Deep vein thrombosis; Disseminated intravascular coagulation; Embolism; Embolism venous; Pulmonary embolism*. This included cases received up to the end of February 2021.

This review identified 114 cases: UK (23), France (20), US (18), Germany (11), Spain (6), Denmark, Italy and Sweden (5 each), Belgium, Canada, Cyprus and Netherlands (2 each); the remaining 13 cases originated from 13 different countries.

Patients' sex was reported in 112 cases; 69 were female and 43 male. Age was reported in 106 cases, and 55 were adult and 51 elderly. There were 125 serious related events reported across the cases. Most frequently reported relevant PTs (>1 occurrence) included: Pulmonary embolism (48), thrombosis (28), Deep vein thrombosis* (23), Thrombophlebitis superficial (6), Venous thrombosis limb (4), Thrombophlebitis and Venous thrombosis (3 each) and Blue toe syndrome and Microembolism (2 each). Event onset ranged from <24 hours to 28 days, with a median onset of 5 days. Of the reported outcomes; fatal (9), resolved/resolving (44), resolved with sequelae (4), not resolved (41) and unknown (29).

Observed/Expected analysis have been performed by Pfizer for Deep vein thrombosis and Pulmonary embolism, neither of which indicate an increased reporting of these events with the vaccine above that expected in the general population.

Table 15. Observed[a] to Expected Ratio of Spontaneously Reported Deep Vein Thrombosis through 28 Feb 2021, Background Rate = 50.00/100,000 PY[b]

	Cumulative (N=35)		Interval (N=23)	
	21-Day Risk Window (3,489,001 PY)	No Risk window (5,777,558 PY)	21-Day Risk Window (1,526,560 PY)	No Risk Window (1,635,967 PY)
Expected cases	1744.5	2888.8	763.3	818
O/E ratio	**0.02**	**0.012**	**0.03**	**0.028**
(95% CI)	0.014, 0.028	0.008, 0.017	0.019, 0.045	0.018, 0.042

a. PT Code: Deep vein thrombosis
b. Heit, 2015[9]

Table 33. Observed[a] to Expected Ratio of Spontaneously Reported Pulmonary Embolus through 28 Feb 2021, Background Rate = 30.00/100,000 PY[b]

	Cumulative (N=60)		Interval (N=48)	
	21-Day Risk Window (3,489,001 PY)	No Risk window (5,777,558 PY)	21-Day Risk Window (1,526,560 PY)	No Risk Window (1,635,967 PY)
Expected cases	1046.7	1733.3	458	490.8
O/E ratio	**0.057**	**0.035**	**0.105**	**0.098**
(95% CI)	0.044, 0.074	0.026, 0.045	0.077, 0.139	0.072, 0.130

a. PT Codes: Pulmonary embolism
b. Heit, 2015[9]

Overall, Pfizer/BioNTech concluded that there was no indication of an increased risk of deep vein thrombosis or pulmonary embolism based on the individual case reports or in the observed/expected analysis.

MHRA's observed vs expected analyses

Data on adverse events requiring hospitalisation have been extracted from England Hospital Episode Statistics admitted patient care data. ICD-10 code lists can be found in Annex 3.

i) *<u>Venous phlebitis and thrombophlebitis including pulmonary embolism</u>*

Figure 1 shows the number of patients (all ages) with a new adverse event within this definition (no event within the preceding 365 days) over time before and during the COVID-19 pandemic.

Figure 1: Patient counts - Venous phlebitis and thrombophlebitis including pulmonary embolism

Table 2: Background rates - Venous phlebitis and thrombophlebitis including pulmonary embolism

Age group	Rates (per 100,000 patient years)
Under 18	
18-49	
50-54	
55-59	
60-64	
65-69	
70-74	
75-79	
80+	

Observed vs expected analyses of the spontaneous reports of venous phlebitis and thrombophlebitis including pulmonary embolism received through the Yellow Card scheme are presented for the Pfizer vaccine in Table 3 (I). The number of observed reports remains substantially below the expected for the Pfizer vaccine and for a 7- and 42-days risk window. Note that the observed will include non-hospitalised cases whereas the expected is based upon the smaller subset of hospitalised cases so will be an underestimate for the total number of expected cases.

Table 3: Observed vs expected analyses - Venous phlebitis and thrombophlebitis including pulmonary embolism

i) Pfizer (1st dose)

Age group	Observed		Expected	
	7 days*	42 days	7 days	42 days
Under 18				
18-49				
50-54				
55-59				
60-64				
65-69				
70-74				
75-79				
80+				
Total**	**50**	**75**	**642**	**3508**

***** Cases with no reported onset date assumed to be within 7 days

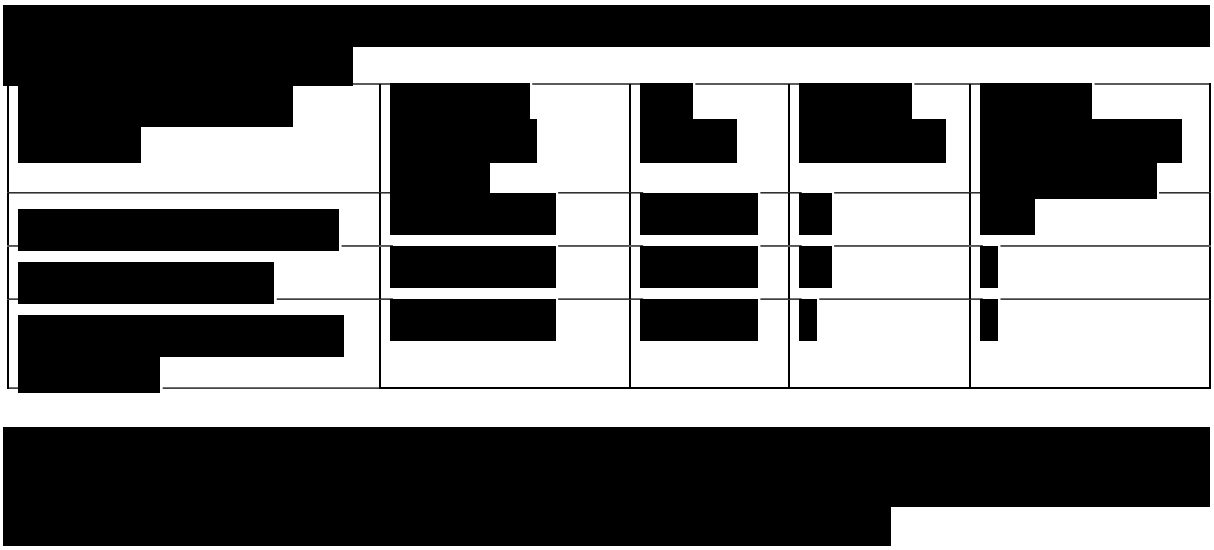
****** Includes cases with unknown age

[redacted] *Epidemiological analysis*

The [redacted] is running rapid cycle analysis of adverse events of special interest in the Vaccine Safety Datalink, using both unvaccinated concurrent comparators and vaccinated concurrent comparators, with data for any mRNA vaccine (Pfizer/BioNTech and Moderna). The data for the analysis as of 13 February 2013 are provided below.

Preliminary results of the unvaccinated concurrent comparator:

[redacted]				
[redacted]				
[redacted]				
[redacted]				



AstraZeneca COVID-19 vaccine and venous thromboembolic events

Up to 14th March 21, MHRA has received the following reports of thromboembolic **events: 202**

Reaction (PT)	No. of events reported
Cerebral venous sinus thrombosis	4
Pulmonary Embolism	65
Deep vein thrombosis	66
Thrombosis	53
Thrombophlebitis	3
Thrombophlebitis migrans	1
Superficial thrombophlebitis	3
Pelvic venous thrombosis	1
Venous thrombosis	3
Thrombosis cerebral	1
Mesenteric vein thrombosis	1
Retinal Vascular Thrombosis	1

N.B. more than one PT can be reported in each case

Gender		Age		Time to onset	
Female	95	Under 20	2	0-6 days	92
Male	102	20-39 years	17	7-14 days	55
Not reported	9	40-59 years	43	>14 days	33
		60-79 years	109	Not reported	21
		80+ years	20		
		Not reported	8		

21 of the cases were fatal. Further details of the cases can be found in annex 6.

4 of the cases reported thrombocytopenia and 3 reported a haemorrhagic event (these cases reported a cerebral venous sinus thrombosis and are further described later in the paper).

AstraZeneca review of thromboembolic events

AstraZeneca provided a review of thromboembolic events in their sPSUR. The search was conducted using the SMQ Embolic and thrombotic events. The search identified 267 cases involving 286 events (PTs) from post marketing sources. 279 events (PTs) were serious and 7 were non-serious. After the search was carried out, two additional cases of pulmonary embolism were identified, as of 10 March 2021.

The reports were received from United Kingdom (246), India (8), Austria (3), France (2), Germany (2), Poland (2), [redacted] (1), [redacted] (1), [redacted] (1), [redacted] (1), [redacted] (1) and [redacted] (1). The 269 cases described 166 females, 95 male and in 8 reports gender was not identified.

Out of the 269 cases, 102 were medically confirmed. 40 events had a fatal outcome.

A batch analysis was performed but this did not identify any patterns in the reported batches.

Observed-to-expected (O/E) analyses were performed for deep vein thrombosis and pulmonary embolism. Background incidence rates were defined by the number of incident reports of a condition or event occurring naturally in the population, expressed in person-time and these background estimates were obtained from the literature. The observed number of cases were found to be significantly less than the expected number of events, the results of the O/E analysis are presented in the table below:

Observed versus expected analysis for Pulmonary embolism and Deep vein thrombosis

Medical Concept	Observed cases	Expected cases	Rate ratio (CI 95%)	Conclusion
Deep vein thrombosis	15	704.87	0.02 (0.01 - 0.04)	Observed significantly < expected
Pulmonary Embolism	22	861.7	0.02 (0.02 - 0.04)	Observed significantly < expected

CI Confidence Interval

AstraZeneca concluded that their review of the cases of Pulmonary embolism (PE)/ Deep vein thrombosis (DVT) indicated no pattern of events and no clustering of risk factors were identified. There were no trends seen for any batches (including ABV5300) that were included in this analyses. The observed number of PE/DVT cases is significantly less than the expected number of events.

MHRA's Observed vs Expected analysis

Observed vs expected analyses of the spontaneous reports of venous phlebitis and thrombophlebitis including pulmonary embolism received through the Yellow Card scheme are presented for the AstraZeneca vaccine in Table 3 (ii). The number of observed reports remains substantially below the expected for the AstraZeneca vaccine and for a 7- and 42-days risk window. Note that the observed will include non-hospitalised cases whereas the expected is based upon the smaller subset of hospitalised cases so will be an underestimate for the total number of expected cases.

ii) AstraZeneca (1st dose)

Age group	Observed		Expected	
	7 days*	42 days	7 days	42 days
[redacted]				
Total**	**128**	**195**	**668**	**3023**

***** Cases with no reported onset date assumed to be within 7 days
****** Includes cases with unknown age

3. Events of thrombocytopenia

Pfizer/BioNTech COVID-19 vaccine and thrombocytopenia

Yellow Card Data
Up to and including 14 March, the MHRA has received a total of 67 cases potentially relating to thrombocytopenia. None of the 67 cases report thromboembolic events occurring alongside the thrombocytopenia or related events. A summary of the events and summary case details reported are provided below.

Reaction (PT)	No. of cases
Platelet count decreased	6
Petechiae	29
Purpura	10
Immune thrombocytopenia	13
Thrombocytopenia	15

Gender		Age		Time to onset	
Female	45	20-39 years	15	0-6 days	36
Male	21	40-59 years	16	7-14 days	8
Not reported	1	60-79 years	10	>14 days	15
		80+ years	13	Not reported	8
		Not reported*	7		

*one case with age reported as 5 years is included in “not reported”

Two fatal cases are included in this series of reports:

- *Immune thrombocytopenia*: [redacted]
- *Platelet count decreased*: [redacted]

Five cases report suspected COVID-19 infection in the past medical history, and one case also reports COVID-19 as an ADR.

Further summary details of these cases can be found in annex 4.

Company review of immune thrombocytopenia

Pfizer/BioNTech have conducted an updated review of thrombocytopenia in the most recent Summary Monthly Safety Report, with a cumulative review of cases up to the end of February 2021. The company identified 67 spontaneous reports of thrombocytopenia were reported between 21 Dec 2020 and 24 Feb 2021. They were all serious cases and included 38 women and 26 men between the ages of 21 and 97 years of age (mean 60.1). Country of case origin: US (25), UK (16), Germany and France (6 each), Belgium, Italy and Spain (2 each) and 1 each from [redacted] There were 8 deaths.

The majority of cases occurred after the first dose of vaccination and within 12 days of vaccination. Two cases were also diagnosed with COVID-19 at the time of the AE.

Case narratives were provided for the 8 fatal cases; none of these report thromboembolic events. The company did not provide details of the other cases to assess whether any of these also reported thromboembolic events.

Pfizer/BioNTech also conducted an observed/expected analysis for thrombocytopenia and this did not indicate a higher reporting rate than that expected in the background population.

Table 1. Observed to Expected Ratio of Spontaneously Reported Thrombocytopenia through 21 Feb 2021, Background Rate = 3.82/100,000PY[a]

	21 Days (2,875,622 PY)	No risk window (4,396,086 PY)
Observed cases[b]	67	67
Expected cases	110	168
O/E	0.610	0.399
(95% CI)	0.473, 0.775	0.309, 0.507

a. Willame, 2020
b. Subsequent to review

MHRA's Observed vs Expected Analysis

Thrombotic thrombocytopenic purpura (TTP)

Figure 2 shows the number of patients (all ages) with a new adverse event of TTP (no event within the preceding 365 days) over time before and during the COVID-19 pandemic.

Figure 2: Patient counts - Thrombotic thrombocytopenic purpura

[redacted] Age-specific background rates are presented in Table 4.

Table 4: Background rates - Thrombotic thrombocytopenic purpura

Age group	Rates (per 100,000 patient years)
[redacted]	[redacted]

Expected counts of are presented in Table 5(I). No reports of TTP have been received for the Pfizer vaccine, so the observed number of cases is 0.

Table 5: Expected counts - Thrombotic thrombocytopenic purpura

i) Pfizer (1st dose)

Age group	Expected*	
	7 days	42 days
[redacted]	[redacted]	[redacted]
Total	1.99	10.36

***** No observed numbers are presented as no cases of TTP have been reported

ii) <u>Idiopathic thrombocytopenic purpura (ITP)</u>

Figure 3 shows the number of patients (all ages) with a new adverse event of ITP (no event within the preceding 365 days) over time before and during the COVID-19 pandemic.

Figure 3: Patient count - Idiopathic thrombocytopenic purpura (ITP)

Background rates for the main and sensitivity analyses are presented in Table 6.

Table 6: Background rates - Idiopathic thrombocytopenic purpura (ITP)

Age group	Rates (per 100,000 patient years)	Sensitivity analysis - Rates (per 100,000 patient years)

Observed vs expected analyses of the spontaneous reports of ITP received through the Yellow Card scheme are presented in Table 7. The number of observed reports remains substantially below the

expected for the main and below the expected for the sensitivity analyses for both vaccines and for a 7 and 42 days risk window.

Table 7: Observed vs expected analyses - Idiopathic thrombocytopenic purpura (ITP)

i) Pfizer (1st dose)

Age group	Observed		Expected		Sensitivity analysis - Expected	
	7 days	42 days	7 days	42 days	7 days	42 days
[redacted]						
Total	6	13	43	233	26	140

[redacted] *Epidemiological analysis for thrombocytopenia AESI*

[redacted]

The [redacted] assessment is also in line with that of the MHRA's epidemiological analysis that the observed reports for ITP and TTP remains substantially below the expected for the main and below the expected for the sensitivity analyses for both vaccines and for a 7 and 42 days risk window. The MHRA's epidemiological analysis for both vaccines is described in further detail in Section 5.

Events of thromboembolic events occurring with thrombocytopenia

AstraZeneca vaccine

Cerebral venous sinus thrombosis

Up to and including 14th March there have been 4 reports of Cerebral venous sinus thrombosis. Ages range from 19- 59 and all events occurred in male patients. All 4 cases report thrombocytopenia (1 case reports immune thrombocytopenia and 3 report thrombocytopenia) as well as cerebral venous sinus thrombosis. No other venous thromboembolic events have been reported in conjunction with thrombocytopenia.

Cases are summarised as follows:

1. [redacted]

2. [redacted]

3. [redacted]

4. 

5. 

Summary of thrombocytopenia events

All events of thrombocytopenia and related events occurring with COVID-19 Astra Zeneca are summarised in this section by reported term.

Up to and including 14 March 2021, the MHRA has received the following Yellow Cards with thrombocytopenia related terms as defined below*:

Reaction (PT)	**No. of cases**
Immune thrombocytopenia	28
Thrombocytopenia	20
Platelet count decreased	9
Petechiae	23
Purpura	11
Thrombocytopenic purpura	3
Severe fever with thrombocytopenia syndrome	3

Reports of Immune thrombocytopenia

28 reports of immune thrombocytopenia (IP) all following the first dose of AstraZeneca COVID-19 vaccine, where stated (24 reports). This is an increase from the 17 cases since the previous review of immune thrombocytopenia on 25 February 2021. One case of immune thrombocytopenia also reports cerebral venous sinus thrombosis along with a cerebral haemorrhage, this case is presented separately above.

Of the 28 reports, age ranged from 19-88 (average age 78). Sex: M (10) F (16) U (2). 2 cases were fatal. Both cases have been considered previously by the EWG at the 25th February meeting.

Age band	Number of cases
Under 20	1
20-39	4
40-59	5
60-79	11
80+	3

Time to onset	Number of cases
0-6 days	10
7-14 days	10
More than 14 days	1
Not reported	7

Reports of thrombocytopenia

There were 20 reports of thrombocytopenia, which is an increase from 5 cases previously reported in the 25th February review. Only 3 reports co-reported immune thrombocytopenia which are included in the above analysis and one also reports thrombocytopenic purpura. 2 cases were fatal. One reported fatal cerebral venous sinus thrombosis along with intracranial haemorrhage and is presented separately. The second case reported inoperable intracranial haemorrhage but contained limited information for assessment. The majority followed the first dose of the vaccine.

Of the 15 reports, age ranged from 32-79 (average age 65). Sex: M (8) F (7).

Age band	**Number of cases**
Under 20	0
20-39	1
40-59	2
60-79	12

80+	0

Time to onset	Number of cases
0-6 days	4
7-14 days	5
More than 14 days	3
Not reported	3

Reports of platelet count decreased

Of the 9 reports of platelet count decreased, 2 reports co-reported immune thrombocytopenia and one report co-reported thrombocytopenia which are included in the above analyses.

Of the 6 remaining reports all following the first dose of AstraZeneca COVID-19 vaccine, where stated (4 reports).

Of the 6 reports, age ranged from 77-85 (average age 80). Sex: F (5) U (1). No cases were fatal.

Age band	Number of cases
Under 20	0
20-39	0
40-59	0
60-79	4
80+	1

Time to onset	Number of cases
0-6 days	4
7-14 days	0
More than 14 days	0
Not reported	2

None of the reports for platelets decreased co-reported thrombotic events or haemorrhagic ADRs.

Reports of petechiae

Of the 23 reports of petechiae, 4 reports co-reported immune thrombocytopenia, 2 reports co-reported thrombocytopenia and one report co-reported platelet count decreased which are included in the above analyses. No cases co-reported thrombotic and/or haemorrhagic ADRs.

Of the 16 remaining reports all following the first dose of AstraZeneca COVID-19 vaccine, where stated (10 reports).

Of the 16 reports, age ranged from 24-86 (average age 62). Sex: M (3) F (12) U (1). No cases were fatal.

Age band	**Number of cases**
Under 20	0
20-39	4
40-59	3
60-79	3
80+	6

Time to onset	**Number of cases**
0-6 days	11
7-14 days	3
More than 14 days	0
Not reported	2

Reports of purpura

Of the 11 reports of purpura, one reports co-reported petechiae and is included in the above analyses.

Of the 10 remaining reports all following the first dose of AstraZeneca COVID-19 vaccine, where stated (8 reports).

Of the 10 reports, age ranged from 27-85 (average age 60). Sex: M (3) F (7) U (1). Two cases were fatal.

[redacted]

Age band	**Number of cases**
Under 20	0
20-39	1

40-59	2
60-79	6
80+	1

Time to onset ranged from 1- 13 days and the breakdown is as follows:

TTO band	**Number of cases**
0-6 days	8
7-14 days	2
More than 14 days	0
Not reported	0

Reports of thrombocytopenic purpura

The 3 reports of thrombocytopenic purpura were reported with immune thrombocytopenia (2 reports) and thrombocytopenia (1 reports) and are therefore included in the above analyses.

Reports of severe fever with thrombocytopenia syndrome

The 3 reports of *s*evere fever with thrombocytopenia syndrome are likely to be due to the patients selecting this term to describe 'severe fever' when submitting a Yellow Card. There is no mention of thrombocytopenia in the case narrative of any of these reports which describe reactogenicity ADRs within a day of receiving the vaccine including shaking and severe fever.

MHRA's Observed vs Expected analysis

Thrombotic thrombocytopenic purpura

Expected counts of are presented in Table 5(ii). No reports of TTP have been received for the AstraZeneca vaccine, so the observed number of cases is 0.

ii) AstraZeneca (1st dose)

Age group	**Expected***	
	7 days	**42 days**
[redacted]		

Total	2.28	9.39

***** No observed numbers are presented as no cases of TTP have been reported

Immune thrombocytopenic purpura

Observed vs expected analyses of the spontaneous reports of ITP received through the Yellow Card scheme are presented in Table 7. The number of observed reports remains substantially below the expected for the main and below the expected for the sensitivity analyses for both vaccines and for a 7- and 42-days risk window.

Table 7: Observed vs expected analyses - Idiopathic thrombocytopenic purpura (ITP)

ii) Pfizer (1st dose)

Age group	Observed		Expected		Sensitivity analysis - Expected	
	7 days	42 days	7 days	42 days	7 days	42 days
Total	6	13	43	233	26	140

iii) AstraZeneca (1st dose)

Age group	Observed		Expected		Sensitivity analysis - Expected	
	7 days*	42 days	7 days	42 days	7 days	42 days
Total**	17	27	43	195	26	117

***** Cases with no reported onset date assumed to be within 7 days
****** Includes cases with unknown age

6. Summary of the MHRA's Epidemiological analysis

Given uncertainty in the case definition of interest as this issue has progressed, a number of separate analyses have been undertaken. These focus on a broader definition of venous phlebitis

and thrombophlebitis including pulmonary embolism, thrombotic thrombocytopenic purpura (TTP), and idiopathic thrombocytopenic purpura (ITP).

Table 1 provides estimates of the manufacturer, age group, and dose specific vaccine exposure up to end 14th March 2021. These data are based on extrapolations of England-wide data (PHE, personal communication). Extrapolations to UK estimates are based on ONS mid-2019 population estimates.

Table 1: Brand specific vaccine exposure data (100,000s)

Pfizer	Age group									Total
	Under 18	18-49	50-54	55-59	60-64	65-69	70-74	75-79	80+	
Number (%) of first doses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	109.1
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(100)
Number (%) of second doses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12.7
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(100)
AZ	**Age group**									**Total**
	Under 18	**18-49**	**50-54**	**55-59**	**60-64**	**65-69**	**70-74**	**75-79**	**80+**	
Number (%) of first doses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	137.0
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(100)
Number (%) of second doses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.5
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(100)

Venous phlebitis and thrombophlebitis including pulmonary embolism

The MHRA has reviewed new adverse events for venous phlebitis and thrombophlebitis (with no event within the preceding 365 days) over time before and during the COVID-19 pandemic. There has been a slight increase in the numbers of cases in the period 2015-2019 which is not entirely accounted for by the increasing population size. Therefore, age-specific background rates have been calculated for 2019 based on the data as presented in Figure 1 and ONS 2019 mid-year population estimates (Table 2). There also appears to have been a slight reduction in the number of cases coinciding with the first lock down period of the pandemic although this rebounded in the months Apr–Dec 2020 to pre-pandemic levels.

Observed vs expected analyses of the spontaneous reports of venous phlebitis and thrombophlebitis including pulmonary embolism received through the Yellow Card scheme are presented for the Pfizer vaccine in Table 3 (I) and for the AstraZeneca vaccine in Table 3 (ii). The number of observed reports remains substantially below the expected for both vaccines and for a 7- and 42-days risk window. Note that the observed will include non-hospitalised cases whereas the expected is based

upon the smaller subset of hospitalised cases so will be an underestimate for the total number of expected cases.

Thrombotic thrombocytopenic purpura (TTP)

The number of cases of TTP have remained reasonably stable in the period 2015-2019 although there is more variability as the incidence rate is generally low. No reports of TTP have been received for either the Pfizer or the AstraZeneca vaccine, so the observed number of cases is 0. The background rates and expected counts for TTP have been provided in Tables 4 and 5 of this paper.

Idiopathic thrombocytopenic purpura (ITP)

The number of cases of ITP was stable in the period 2015-2019. There also appears to have been a marked reduction in the number of cases coinciding with the first lock down period of the pandemic which rebounded slightly in the months Apr–Dec 2020 but is not yet at pre-pandemic levels. Therefore, based on these data, a sensitivity analysis assuming a background rate = 60% of pre-pandemic rates (~200/350). Background rates and sensitivity analyses for these are presented in Table 6.

The number of observed spontaneous reports of ITP received through the Yellow Card scheme remains substantially below the expected for the main and below the expected for the sensitivity analyses for both vaccines and for a 7 and 42 days risk window (Table 7).

Discussion

There is considerable uncertainty around the signal raised by EU member states and PRAC in terms of definition of cases to be considered as part of the signal review. Limited details are available from the cases reported in EU member states. Given this uncertainty, the review broadly considers two separate analyses. The first is of thromboembolic events occurring in relation to the COVID-19 vaccines currently in use in the UK, and the second is of events of thromboembolic events occurring concurrent to events of thrombocytopenia.

None of the epidemiological analyses suggest an increased risk of venous phlebitis and thrombophlebitis including pulmonary embolism, thrombotic thrombocytopenic purpura, or idiopathic thrombocytopenic purpura with either vaccine. We would likely expect reporting to be high for serious events, particularly close to vaccination, although there is uncertainty around the extent of this under-reporting.

<u>Thromboembolic events generally</u>

With regard to thromboembolic events more generally, no specific clusters or patterns were seen with either vaccine. For Pfizer/ BioNTech, one fatal case of pulmonary embolism also reports haematemesis but this is likely related to the severe vomiting also reported in this case. Across the thromboembolic and thrombocytopaenia events reported in the Yellow Card data there tends to be a short time to onset of less than a week, and the company data also suggested shorter time to onset in the cases identified in their reviews. This is not likely to be supportive of vaccine-specific role in these events. There is also no strong pattern in the cases identified for Pfizer/BioNTech suggesting any trends relating to prior COVID-19 infection or for reactions post-second dose to indicate a “priming” with these factors.

Both the company and [redacted] epidemiological analysis do not raise any statistically significant signals for the thromboembolic or thrombocytopenic events analysed. The company analysis of global spontaneous data for thrombocytopenia and thromboembolic events also did not raise any signals.

For the AstraZeneca vaccine, most reports of these events have a shorter time to onset of under 7 days. The pattern of ages in which these events are reported is in keeping with the expected background trend of these events, in that they increase with age, as well as the exposure of the vaccine in different age groups; numbers dip in the 80+ age group, which corresponds with the fact that fewer patients in this age group have received the AstraZeneca vaccine compared to all other age brackets. Although numerically there appear to be more events of PEs and DVTs occurring with AstraZeneca compared to Pfizer, it is noted that usage of the AstraZeneca vaccine is higher amongst the 55-75 age groups when incidence of naturally occurring venous thromboembolic events start to increase. Both MHRA and AstraZeneca observed vs expected analyses find that the observed number of cases is smaller than the expected number for a vaccinated population of this size.

Thromboembolic events occurring in conjunction with thrombocytopenia

With regard to thrombocytopenic events with associated thromboses (particularly venous sinus thromboses), it remains unclear at present if this is driven by any one unifying diagnosis for thrombocytopenic events, and if this is causally associated with the vaccines. Proposed mechanisms include the possibility of a HITT-like, ITP or TTP type event, although this is extremely challenging to ascertain purely from the reports received. Although some reporters will have sought a specialist haematologist opinion prior to reporting, it is possible that this was not the case for all and thus not all possible alternative diagnoses may have been considered when reporting thrombocytopenia. There remain a small number of cases with onset after a few days and with a lack of alternative aetiology, however evaluation is limited by uncertainty about a plausible time to onset given the unknown mechanism and underlying event, as well as limited information about other plausible causes. It is equally possible that reports may represent an entirely new event that does not fit into any currently known pathology or condition. Regardless of the potential mechanism, considering usage, venous thromboembolic events reported in conjunction with thrombocytopenia remains extremely rare with these vaccines.

There appears to be a pattern of events emerging from EU member states of cerebral venous sinus thromboses occurring in conjunction with thrombocytopenia in younger individuals. It is unclear why any potential induced hypercoagulable state would result selectively in events of venous sinus thrombosis alone. It is also possible that these have been detected more readily than other peripheral venous thromboembolic events as they may have more quickly led to very evident neurological events. Bias is identification and reporting of cases post-vaccine therefore remains a possibility in this apparent cluster of cases.

For the Pfizer/BioNTech COVID-19 vaccine, there are no cases reporting venous thromboembolic events alongside thrombocytopenia, including in the two reports of cerebral venous sinus thrombosis.

There have been 4 cases reported with the AstraZeneca vaccine which appear to have similar clinical details to the cases reported from EU member states, these cases are reported in younger patients (ages [redacted] and all 4 also report a finding of thrombocytopenia or immune thrombocytopenia. Where time to onset of the event was stated, in the UK cases this appears to have occurred within 1-3 days, while where stated the cases from [redacted] indicate a slightly longer onset time of 6 – 10 days. In the UK the incidence of this remains exceedingly low at approximately 4 reports per 11 million doses administered. Of note this incidence is lower than the natural incidence of cerebral venous sinus thrombosis of 5-16 per million. The reporting rate appears to be higher in EU member states with around 4 per million doses from [redacted] and approximately 1 per 100,000 in [redacted]

7. Conclusions

Overall, there is currently insufficient evidence to support a causal association with the Pfizer vaccine with either thrombocytopenia or thromboembolic events. There is also no evidence for an association with events involving combined venous thromboembolism and thrombocytopenia.

With Astra Zeneca the pattern seen with venous thromboembolic events more generally is in keeping with expected background trends and usage of the vaccine. There have been a small number of cases reported of thromboses with thrombocytopenia which appear to be in keeping with the cases reported from the EU, however this remains at a low incidence given the usage to date. The available evidence is insufficient to establish a causal association, and MHRA continues to monitor cases reporting thrombocytopenia, immune thrombocytopenia and associated events.

In summary, venous thromboembolism (VTE) occurs naturally, in all ages, and is not uncommon. We have been closely reviewing reports of VTE and their consequences following vaccination with COVID 19 vaccines. Amongst the more than 24 million doses of both vaccines administered so far[2], several hundred cases of VTE are expected to have occurred by chance within a short time after vaccination. Our analyses show no evidence that VTE, overall, is occurring more than would be expected in the absence of vaccination, for either vaccine.

The action taken by some EU countries over the past week to temporarily pause the use of the AstraZeneca vaccine has been based mainly on isolated reports of cerebral sinus vein thrombosis concurrent with thrombocytopenia and bleeding shortly after vaccination. This form of blood clot can also occur naturally in the absence of vaccination, can occur in association with COVID disease and is extremely rare, and a causal association with the vaccine has not been established. The reporting rate of this following vaccination in [redacted] has been 4 per million doses of the vaccine. In the UK, we have so far identified 4 possible cases of this form of blood clot with low platelets after 11 million doses of the AstraZeneca vaccine.

Whilst this requires further review, a causal association with the vaccine cannot be established based on available information. Given the extremely rare rate of occurrence of these events, the benefits of the AstraZeneca COVID vaccine, with the latest data suggesting an 85% reduction in hospitalisation and death from COVID disease, far outweigh any possible risks of the vaccine.

The most common side effects of any COVID vaccine are injection site reactions and a mild 'flu-like illness', such as headache, chills, muscle aches and fever. These generally appear within a few hours, last no more than a day or two but not everyone will experience this. Anyone with severe or persistent headaches that last for more than a few days after vaccination, or who experience generalised bruising beyond the site of vaccination after a few days, should seek medical attention to ensure that other illness unrelated to vaccination can be treated.

8. Advice sought from the EWG

1. Does the EWG agree with the above conclusions?

2. Does the EWG consider that the reports of cerebral venous sinus thrombosis concurrent with thrombocytopenia suggest a safety signal with either the AstraZeneca vaccine, and or the Pfizer (or other) COVID vaccines that requires further evaluation? If so, what is the best case definition and what further investigation should be undertaken to evaluate the signal?

[2] Vaccinations | Coronavirus in the UK (data.gov.uk)

Specifically, can the EWG advise on:

a) any further relevant data sources
b) the codes / or definition used to identify relevant events in electronic and administrative healthcare record databases

3. Does the EWG consider that any regulatory action is required at this stage, including any risk mitigating advice or updates to the product information for either vaccine at this stage?

Annex 1

Cases from [redacted]

Covid-19 vaccine Astra Zeneca: Cluster of serious and rare thromboembolic events in young people

Reason

[redacted] has additional information relating to the signals of ITP and thrombotic and embolic events, combined.We have received several concerns from our leading clinical experts regarding what they consider to be a cluster of exceptional events in young persons seen in temporal relationship with covid-19 vaccine AstraZeneca.We have recently received three ICSRs from healthcare professionals regarding young people who has received the Astra Zeneca-vaccine, and we have been notified via phone from the Intensive Care Units regarding one additional young person with similar reactions. These ICSRs has been received, but not yetbeen assessed and distributed to EudraVigilance. The ICSR will be sent to EV as soon as possible.

Case 1 (authority numb: [redacted]) The case is concerning a [redacted]

Case 2 (Authority numb [redacted] is a fatal case regarding a [redacted]

Case 3 (Authority number: [redacted]): [redacted]. [redacted]

[redacted]

Case 4: [redacted]

Patient reports

[redacted] has additionally received two patient reports with information of symptoms that could indicate thrombocytopenia and/or ITP. The two reports has been received, but has not yet been assessed and distributed to EudraVigilance.

Case report 1: [redacted]

Case report 2:

[redacted]

[redacted]

[redacted]

Overall conclusion

Based on the currently available information, the newly received cases appears to follow a similar pattern as also seen in cases of similar events reported from [redacted] Thus, it is considered that these cases strenghtens the signal of thromboembolic events and ITP/Thrombocytopenia with the Covid-19 AstraZeneca vaccine.

Vaccination with Covid-19 vaccine Astra Zeneca is on hold in [redacted] as of 11th of March, and thus no regulatory action has been taken yet. [redacted] will continue to consider the need for regulatory action as more information from our investigation becomes available.

Action taken

Due to the above mentioned reports the following actions have been taken:

-Additional information regarding the above mentioned cases is being collected

- [redacted] is working on identifying the batch number for all the above mentioned cases, to investigate a potential batch related issue. We already have information that two different batches are involved.

- A press conference and press release regarding the cases and the ongoing investigation has been released.

- The press release also contains information advising young persons with petechiaes and signs and symptoms of thromboembolic events following vaccination to immediately seek medical attention.

- [redacted] is trying to get directly into contact with the patients that has sent reports of bruising to ensure that they seek medical attention as soon as possible.

- [redacted] will continue to consider the need for regulatory action as more information from our investigation becomes available.

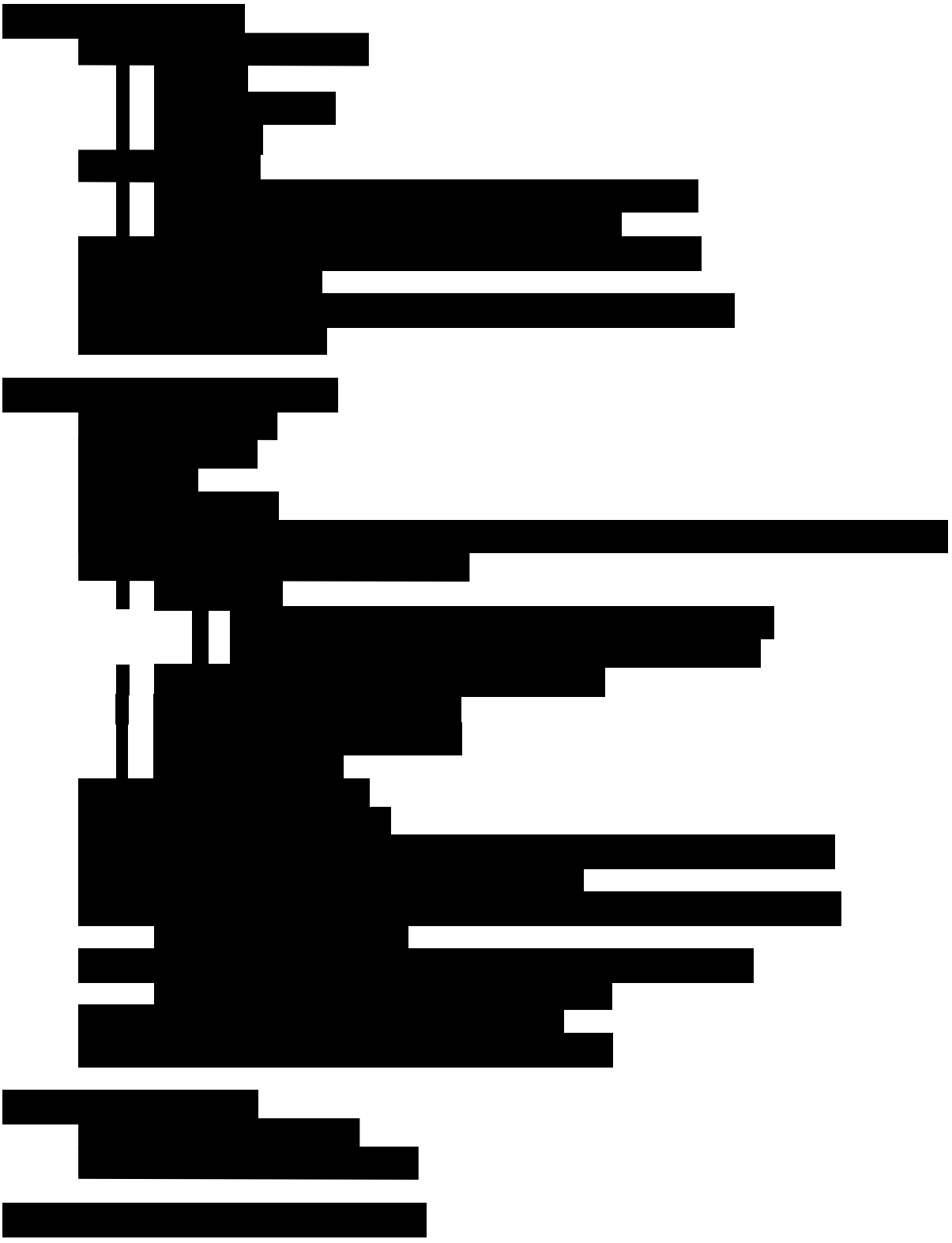
Annex 2

Secondary care – ICD-10

[redacted]

Annex 3: ICD-10 code lists for observed vs expected analyses

Venous phlebitis and thrombophlebitis including pulmonary embolism



Annex 4 – Summary of Pfizer/BioNTech cases for thrombocytopenia and related events

Immune thrombocytopenia

There have been a total of 13 reports of immune thrombocytopenia reported with the Pfizer/BioNTech vaccine up to and including 14 March 2021. None of these are fatal. One of these reports intracranial haemorrahage with the immune thrombocytopenia and one further case each reports muscosal bleeding and epistaxis. None of these cases report thromboembolic events.

Summary of immune thrombocytopenia cases with Pfizer/BioNTech, as of 14 March 2021

Gender		Age		Time to onset	
Female	9	20-39 years	4	0-6 days	5
Male	4	40-59 years	1	7-14 days	3
		60-79 years	5	>14 days	3
		80+ years	3		
		Not reported	-		

None of the cases are reported after the second dose of the vaccine.

Thrombocytopenia

There has been a total of 15 cases reporting thrombocytopenia with the Pfizer/BioNTech COVID-19 vaccine, one of which is reported with immune thrombocytopenia and is included above. Of the remaining 14 cases, there is one fatal case in [redacted]

There is also one case reporting intracranial hemorrhage, posterior reversible encephalopathy syndrome and upper gastrointestinal hemorrhage and one case reporting mucosal bleed. There are no other cases suggesting serious bleeding events.

None of these cases report thromboembolic events.

Summary of thrombocytopenia cases with Pfizer/BioNTech, as of 14 March 2021

Gender		Age		Time to onset	
Female	7	20-39 years	1	0-6 days	5
Male	6	40-59 years	1	7-14 days	3
Unknown	1	60-79 years	7	>14 days	3
		80+ years	3	Not reported	3
		Not reported	2		

One case in a patient with [redacted]

None of the cases were reported following a second dose of the vaccine, and none reported prior or concurrent COVID-19 infection.

Platelet count decreased

There has been a total of 6 reports of platelet count decrease with the Pfizer/BioNTech vaccine up to 14 March 2021. One of these is already included in the report of immune thrombocytopenia and thrombocytopenia above. None of these cases report concurrent thromboembolic events.

Of the remaining 5 cases, one is a fatal report [redacted]

Three of these cases were in male patients and 2 in female patients. Two of the cases were aged 60-79 years and three were over 80 years old. [redacted]

Purpura

The MHRA has received 10 cases of purpura with the Pfizer/BionTech COVID-19 vaccine, up to and including 14 March. None of these cases are fatal. None of the cases are reported after the second dose of the vaccine. One reports [redacted] Prior suspected COVID-19 infection is reported in two cases one 9 months and one 12 months prior to vaccination. No other cases report potential confounding factors. One case reports haematemesis, no other cases indicate serious bleeding events. None of these cases report thromboembolic events.

Summary of purpura cases with Pfizer/BioNTech, as of 14 March 2021

Gender		**Age**		**Time to onset**	
Female	7	20-39 years	3	0-6 days	6
Male	3	40-59 years	3	7-14 days	1
Unknown	-	60-79 years	1	>14 days	1
		80+ years	2	Not reported	2
		Not reported	1		

Petechiae

The MHRA has received 29 cases of petechiae with the Pfizer/BionTech COVID-19 vaccine, up to and including 14 March. Two of these cases are also reported under immune thrombocytopenia, one under thrombocytopenia and one under purpura. The remaining 25 cases are summarised here. None of the cases report thromboembolic events.

None of the cases are fatal. One case also reports vaginal haemorrhage and haematuria in a [redacted] but limited details on these events haemorrhagic events provided. [redacted]

Four cases report suspected COVID-19 infection in the history; two concurrent with the suspected reactions, one 10 days prior to the reactions and one 10 months prior to the events.

One reporting rash and petechia [redacted].

Summary of petechiae cases with Pfizer/BioNTech, as of 14 March 2021

Gender		**Age** *		**Time to onset**	
Female	20	20-39 years	7	0-6 days	19
Male	5	40-59 years	11	7-14 days	2
Unknown	-	60-79 years	7	>14 days	4
		80+ years	2	Not reported	1
		Not reported	3		

*one age reported as 5 years has not been included as it is considered improbable

Annex 5 – Summary of Pfizer/BioNTech Venous thromboembolic Yellow Card reports

Cerebral venous sinus thrombosis

There have been two UK reports of cerebral venous sinus thrombosis following administration the Pfizer vaccine, neither of which report concurrent thrombocytopenia or bleeding events which could be indicative of thrombocytopenia.

These cases are summarised below:

- [redacted]

Pulmonary Embolism

There has been a total of 34 cases of pulmonary embolism reported with the Pfizer/BioNTech COVID-19 vaccine. An overview of details of these cases are summarised in the below table. One of these cases is fatal:

- [redacted]

[redacted] ***Assessor comment***: this case potentially represents bleeding events (haematemesis) with a thromboembolic event, however the haematemesis is likely secondary to the severe vomiting. Concurrent COVID-19 infection may also be a confounding factor, although this was asymptomatic.

Summary of cases – Pulmonary Embolism with Pfizer/BioNTech COVID-19 vaccine

Gender	
Female	16
Male	15
Unknown	3
Age	
20-39 years	6
40-59 years	12
60-79 years	9
80+ years	2
Not reported	-
Time to onset	
0-6 days	16
7-14 days	8
>14 days	7

Four of these cases are following the second dose of the vaccine; three of these don't report the date of the first vaccine and one is a fatal case [redacted]

Fourteen of these cases report possible confounding factors: psoriatic arthropathy, psoriasis, COPD (n=2), Facioscapulohumeral muscular dystrophy, DVT, asthma, embolism, renal infarct, chronic lymphocytic leukaemia, pulmonary embolism (n=2, although possible misclassification), pneumonia with pulmonary embolism, and hip arthroplasty. Further to this, four cases report pneumonia as ADRs and one reports COVID-19 as an ADR.

Prior COVID-19 infection is reported in 3 of the cases, however all of these appear to be concurrent infections with the COVID-19 start dates same day, 1 day and 4 days post vaccination.

Other than the fatal case there are no other cases reporting bleeding events, and no cases indicating thrombocytopenia.

Deep vein thrombosis

There has been a total of 16 UK reports which include the event deep vein thrombosis with the Pfizer/BioNTech vaccine; two of these are included in the analysis of pulmonary embolism above and

are not further discussed. The remaining 14 cases are summarised below. None of these cases reported thrombocytopenia, or bleeding events which might be suggestive of thrombocytopenia.

Summary of cases – Deep vein thrombosis with Pfizer/BioNTech COVID-19 vaccine

Gender	
Female	8
Male	6
Unknown	-
Age	
20-39 years	-
40-59 years	5
60-79 years	4
80+ years	5
Not reported	-
Time to onset	
0-6 days	8
7-14 days	2
>14 days	4

Possible confounding factors were identified in 7 cases: gastric cancer and hypertension, Antithrombin III deficiency and ex-smoker, chemotherapy for brain neoplasm and has pneumonia, osteoarthritis and osteoporosis (unknown if the patient has received surgery), DVT (n=2, possible misclassification), BMI of 31.

None of the cases reported prior or concurrent COVID-19 infection. Two of these cases were reported after the second dose of the vaccine. One with a time [redacted]

Thrombosis

There has been a total of 18 UK reports for Pfizer/BioNTech including the PT thrombosis; three of these are described above in one case of pulmonary embolism, one case of DVT and one case reporting pulmonary embolism, vena cava embolism and vena cava thrombosis. The remaining 15 cases include one fatal case of thrombosis and myocardial infarction and this is summarised below:

- [redacted]

None of these cases report thrombocytopenia or bleeding terms which may indicate thrombocytopenia.

Summary of cases – Thrombosis with Pfizer/BioNTech COVID-19 vaccine

Gender	
Female	8
Male	7
Unknown	-
Age*	
20-39 years	2
40-59 years	1
60-79 years	4
80+ years	5
Not reported	2
Time to onset	
0-6 days	11
7-14 days	3
>14 days	1

*[redacted]

Possible confounding factors in were reported in 6 cases:

- Alcoholism, Dysphagia, Hepatic cirrhosis, COPD, Pancreatitis chronic, Osteoarthritis, Asbestosis, Metastases to liver
- Carotid artery disease, Chronic kidney disease, Arthritis, Hypertension, Ex-tobacco user, Hip arthroplasty, Back injury, Carotid artery stenosis, Spinal operation, Transient ischaemic attack
- Suspected COVID-19 approximately 2 weeks prior to reaction, Rheumatoid arthritis
- Thrombosis (possible misclassification)
- Hepatic function abnormal, Deep vein thrombosis, Renal impairment, Thrombosis, Neuropathy peripheral
- Gastrointestinal carcinoma

Two cases report suspected COVID-19 infections, both two weeks prior to vaccination.

None of these cases are reported after the second dose of the vaccine.

Additional thromboembolic terms of interest

Several other venous thrombosis related terms have been reported and are described below. None of these report thrombocytopenia or bleeding disorders suggestive of thromboembolism.

- Five reports of thrombophlebitis have been received with the Pfizer/BioNTech vaccine, all of which are in females. None of these cases report events associated with thromboembolism or bleeding. One is aged 20-39 years, one 40-59 years, one 60-79 years and two are 80+ years. Three of the cases had time to onset of 0-6 days and one each for 7-14 days and >14 days. One of these cases reported pre-existing varicose veins but no other cases reported relevant past medical history. None of the cases reported prior or concurrent COVID-19 infection.
- One report of superficial thrombophlebitis reported with DVT and is discussed under that section above.

- One case reporting pelvic venous thrombosis and abdominal pain [redacted]
- One report of venous thrombosis in [redacted]
- One case of pulmonary thrombosis [redacted]
- One case of pulmonary infarct which also reports pulmonary embolism, thrombosis and vena cava embolism, is included in the above analysis.
- One report including both PTs cerebellar stroke and embolic stroke, along with atrial fibrillation, dizziness and vomiting [redacted]

Annex 6 AstraZeneca thromboembolic event cases.

Pulmonary embolism (PE)

There have been 65 reports of pulmonary embolism (PE). Age ranges from 19-94 (average age 65). Sex: M (31) F (30) U(4). 9 cases were fatal.

Age band	Number cases
Under 20	1
20-39	2
40-59	15
60-79	35
80+	8

Time to onset ranged from 1- 47 days and the breakdown is as follows:

TTO band	Number cases
0-6 days	31
7-14 days	17
More than 14 days	12
Not reported	5

18 cases reported a confounding factor:

- 2x Mobility decreased (with other comorbidities),
- fall prior to vaccine,
- Concurrent COVID-19 infection,

- onset of symptoms (SOB) prior to vaccination,
- 5x cancer/cancer progression,
- AF and congestive cardiac failure,
- 5 x Prior PE
- Recent surgery
- Heart disease
- Morbidly obese

In addition to this, 5 patients reported having a prior COVID-19 infection .

None of the cases reported thrombocytopenia and none reported a haemorrhagic event.

Fatal cases

There were 9 fatal cases with PE. 7 female patients and 2 male, ages 19-94.

[redacted]

[redacted]

Deep Vein Thrombosis (DVT)

There are 66 cases of DVT. 4 co-report PE. Ages range from 25-99 (average age 65).

Age band	Number cases
Under 20	0
20-39	7
40-59	8
60-79	42
80+	7
Unknown	2

Sex: M (31) F (35) U(4). 4 cases were fatal (3 of which co-reported PE and are covered above).

Time to onset ranged from 1- 47 days and the breakdown is as follows:

TTO band	Number cases
0-6 days	30
7-14 days	19
More than 14 days	12
Not reported	5

None of the cases reported thrombocytopenia and none reported a haemorrhagic event.

20 cases report confounding factors:

- 2x Concurrent COVID-19 and breast cancer (in one case)
- fall prior to vaccine,
- Testis cancer, Metastases to liver
- 2x Sarcoidosis
- Protein S deficiency, Thrombosis
- Previous damage to vascular system following a fall
- antiphospholipid syndrome
- Factor V Leiden
- Arthritis
- BMI 34
- prothrombin deficiency and previous VTE
- Cerebrovascular accident, Non-Hodgkin's lymphoma
- factor V deficiency

- recent knee surgery
- previous DVT
- protien c deficiency and factor v leiden
- Prostate cancer and Rheumatoid arthritis
- Rheumatoid arthritis and IBD

6 cases reported having a prior COVID-19 infection.

Fatal cases

There were 4 fatal cases with DVT. 3 female patients and 1 male, ages 62-94 (average 75).

[redacted]

The remaining fatal DVT case [redacted]

Thrombosis

There have been 53 reports of the PT "thrombosis". Age ranges from 30-92 (average age 61). Sex: M (28) F (24) U(1). 5 cases were fatal.

Age band	Number cases
Under 20	0
20-39	5
40-59	16
60-79	23
80+	5
Unknown	4

Time to onset ranged from 1- 64 days and the breakdown is as follows:

TTO band	Number cases
0-6 days	23
7-14 days	11
More than 14 days	8
Not reported	11

8 cases reported a confounding factor:

- History of blood clots
- 2x Rheumatoid arthritis
- End stage renal disease
- Myocardial infarction and heart valve replacement

- Underactive thyroid and hashimoto's disease
- High cholesterol
- Hypertension, Acute myocardial infarction, Left ventricular dysfunction, Pericarditis

In addition to this, 5 patients reported having a prior COVID-19 infection.

None of the cases reported thrombocytopenia and none reported a haemorrhagic event.

Fatal cases

There were 5 fatal cases. 1 female patient and 4 male, ages 42-74.

[redacted]

Thrombophlebitis

There have been 7 reports of thrombophlebitis (includes "thrombophlebitis" (3); "thrombophlebitis superficial (3)"; "thrombophlebitis migrans" (1)). Age ranges from 59-76 (average age 66). Sex: M (5) F (2). 0 cases were fatal.

Age band	**Number cases**
Under 20	0
20-39	0
40-59	1
60-79	6
80+	0

Time to onset ranged from 1- 11 days and the breakdown is as follows:

TTO band	**Number cases**
0-6 days	5

7-14 days	2
More than 14 days	0
Not reported	0

3 cases reported a confounding factor:

- Varicose veins (2 cases)
- History of blood-clotting disorders (1 case with Factor V Leiden deficiency)

None of the cases reported having a recent prior COVID-19 infection.

Zero cases co-report either thrombocytopenia or a haemorrhagic event with the thrombotic event.

Fatal cases

There were zero fatal cases with thrombophlebitis.

PELVIC VENOUS THROMBOSIS

1 report of pelvic venous thrombosis (MedDRA PT)

[redacted]

Confounding factors – medical history of obesity, hypertension, diabetes and taking statins.

VENOUS THROMBOSIS

There have been 3 reports of venous thrombosis (MedDRA PT) (4 cases in total on database – one is a duplicate case). All first dose. Two cases ages: 36 and 61 years old. Unknown age in one case. All male cases. 1 fatal case.

Age band	**Number cases**
Under 20	0
20-39	1
40-59	0
60-79	1
80+	0

Time to onset ranged from 9 – 16 days and the breakdown is as follows:

TTO band	**Number cases**
0-6 days	2
7-14 days	1 *

More than 14 days	0
Not reported	0

[redacted]

Confounding factors (1 case report potential confounding factors)

- DVT (following long haul flight) and varicose veins

Co-reported haematological terms

- 1 case co-reports phlebitis in [redacted]

Fatal case

One case

[redacted]

CEREBRAL VENOUS SINUS THROMBOSIS

There have been 4 reports of cerebral venous sinus thrombosis (MedDRA PT). Age range from 19 to 59 years old (average age: 33.5). All male cases. 1 fatal case.

Age band	**Number cases**
Under 20	1
20-39	2
40-59	1
60-79	0
80+	0

Time to onset ranged from 9 – 16 days and the breakdown is as follows (data for 3 reports):

TTO band	**Number cases**
0-6 days	0
7-14 days	2
More than 14 days	1
Not reported	0

Confounding factors (2 cases report potential confounding factors)

- Ventricular septal defect reported [redacted]
- Unconfirmed malignancy

Co-reported haematological terms

- 1 case co-reports low platelet count
- 1 case co-reports thrombocytopenia, multiple areas of intracerebral haemorrhage together with a venous sinus thrombosis (fatal case)
- 1 case mentions the patient was noted to have a thrombocytopenia of unknown aetiology however it is not clear in the report whether this was pre-existing or considered an adverse event
- 1 case co-reports immune thrombocytopenia and intracranial bleeding

Fatal case

1 fatal case.

[redacted]

[redacted]

Thrombosis cerebral

There has been 1 fatal report of thrombosis cerebral

[redacted]

Retinal Vascular Thrombosis

There has been 1 retinal vascular thrombosis

[redacted]

Mesenteric vein thrombosis

There has been 1 report of mesenteric vein thrombosis

[redacted]

Annex 6- EMA statement on thromboembolic events

EMA's safety committee continues investigation of COVID-19 Vaccine AstraZeneca and thromboembolic events – further update

News 15/03/2021

Several authorities responsible for national vaccine campaigns in EU countries have temporarily paused vaccination with COVID-19 Vaccine AstraZeneca. This is a precaution taken in the light of their national situation while EMA investigates a number of events of blood clots in people who had received the vaccine, as previously reported.

Events involving blood clots, some with unusual features such as low numbers of platelets, have occurred in a very small number of people who received the vaccine. Many thousands of people develop blood clots annually in the EU for different reasons. The number of thromboembolic events overall in vaccinated people seems not to be higher than that seen in the general population.

EMA is working closely with the company, with experts in blood disorders, and with other health authorities including the UK's MHRA based on its experience with around 11 million administered doses of the vaccine.

EMA's investigation has been continuing over the weekend, and rigorous analysis of all the data related to thromboembolic events will be carried out in the coming days. Experts are looking in great detail at all the available data and clinical circumstances surrounding specific cases to determine whether the vaccine might have contributed or if the event is likely to have been due to other causes. EMA's safety committee (PRAC) will further review the information tomorrow (Tuesday) and has called an extraordinary meeting on Thursday 18 March to conclude on the information gathered and any further actions that may need to be taken.

The COVID-19 pandemic is a global crisis, with devastating health, social and economic impact, and continues to be a major burden on EU health systems. Vaccines for COVID-19 help to protect individuals from becoming ill, especially healthcare professionals and vulnerable populations, such as older people or those with chronic diseases. While its investigation is ongoing, EMA currently remains

of the view that **the benefits of the AstraZeneca vaccine in preventing COVID-19, with its associated risk of hospitalisation and death, outweigh the risks of side effects**.

EMA will continue to communicate further as appropriate. In the meantime, anyone who has received the vaccine and has any concerns should contact an appropriate healthcare professional. It is important that people who suspect they may have a side effect after vaccination report this to the national medicines regulator, or to a healthcare professional who can help them do so.

More about the medicine

COVID-19 Vaccine AstraZeneca is a vaccine for preventing coronavirus disease 2019 (COVID-19) in people aged 18 years and older. COVID-19 is caused by SARS-CoV-2 virus. COVID-19 Vaccine AstraZeneca is made up of another virus (of the adenovirus family) that has been modified to contain the gene for making a protein from SARS-CoV-2. COVID-19 Vaccine AstraZeneca does not contain the virus itself and cannot cause COVID-19.

The most common side effects with COVID-19 Vaccine AstraZeneca are usually mild or moderate and improve within a few days after vaccination.

More about the procedure

The review of thromboembolic events with COVID-19 Vaccine AstraZeneca is being carried out in the context of a safety signal, under an accelerated timetable. A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine such as a vaccine and that warrants further investigation.

The review is being carried out by EMA's Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines. Once the review is completed, PRAC will make any recommendations necessary to minimise risks and protect patients' health.