Update on COVID-19 AZ vaccine: Thromboembolic events with thrombocytopenia

VBR EWG 6 April 2021 (data lock: 31 March 2021)

Medicines & Healthcare products Regulatory Agency

Background

Ongoing, detailed review of reports of very rare events of thromboembolic events (including CVST and other events) with concurrent thrombocytopenia.

Assessment of Yellow Card Scheme reports against a case definition developed with independent expert advice.

Latest consideration at CHM and Vaccine Benefit Risk Expert Working Group (EWG) meetings:

- 27 March: CHM meeting
- 31 March: Vaccine Benefit Risk EWG meeting
- 1 April: CHM meeting
- 4 April: CHM meeting

Summary of case reports (data lock 31 Mar 2021)

79 cases of thromboembolic events with thrombocytopenia including confirmed, probable or possible cases (51 female, 28 male):

- 44 CVST (mean age 44.2 years; range 18-79 years [n=37]), 14 fatal (32%)
- 35 non-CVST (mean age 50.5 years; range 21-73 years [n=30]), 5 fatal (14%)

Case definition		Number of cases	Number of fatalities
Confirmed	Probable + PF4 antibodies	9	2
Probable	Possible + D-dimer >4000 ng/mL	14	0
Possible	Venous/arterial thrombosis + TCP	56	17
	Totals	79	19
	Overall case fatality rate	24%	

Comparative exposure data – AZ 1st doses

Age group	Estimated number of first AZ doses in UK (1,000,000s)	%
15-19 years	[redacted]	[redacted]
20-24 years	[redacted]	[redacted]
25-29 years	[redacted]	[redacted]
30-34 years	[redacted]	[redacted]
35-39 years	[redacted]	[redacted]
40-44 years	[redacted]	[redacted]
45-49 years	[redacted]	[redacted]

Age group	Estimated number of first AZ doses in UK (1,000,000s)	%
50-54 years	[redacted]	[redacted]
55-59 years	[redacted]	[redacted]
60-64 years	[redacted]	[redacted]
65-69 years	[redacted]	[redacted]
70-74 years	[redacted]	[redacted]
75-79 years	[redacted]	[redacted]
80+ years	[redacted]	[redacted]

(data lock 31st March)

Incidence rate – CVST by age

Age group	Estimated number of first doses in UK (1,000,000s)	Total number of cases	Case incidence rate (per 1 million doses)	Exc. unlikely cases	Case incidence rate (per 1 million doses)	Number of fatal cases (inc. unlikely)	Fatal incidence rate (per 1 million doses)
15-29 yrs	[redacted]	9	[redacted]	8	[redacted]	4	[redacted]
30-39 yrs	[redacted]	10	[redacted]	9	[redacted]	5	[redacted]
40-49 yrs	[redacted]	6	[redacted]	6	[redacted]	1	[redacted]
50-59 yrs	[redacted]	11	[redacted]	8	[redacted]	2	[redacted]
60-69 yrs	[redacted]	4	[redacted]	4	[redacted]	3	[redacted]
70-79 yrs	[redacted]	2	[redacted]	2	[redacted]	0	[redacted]
Total	20.2	49*	2.4 (1.8,3.2)	44*	2.2 (1.6,2.9)	17**	0.8 (0.5,1.4)

* Includes 7 – unknown age, ** Includes 2 – unknown age

(data lock 29th March)

Incidence rate – CVST + other TE by age

Age group	Estimated number of first doses in UK (1,000,000s)	Total number of cases	Case incidence rate (per 1 million doses)	Exc. unlikely cases	Case incidence rate (per 1 million doses)	Number of fatal cases (inc. unlikely)	Fatal incidence rate (per 1 million doses)
15-29 yrs	[redacted]	12	[redacted]	11	[redacted]	4	[redacted]
30-39 yrs	[redacted]	18	[redacted]	16	[redacted]	7	[redacted]
40-49 yrs	[redacted]	10	[redacted]	10	[redacted]	2	[redacted]
50-59 yrs	[redacted]	16	[redacted]	12	[redacted]	3	[redacted]
60-69 yrs	[redacted]	14	[redacted]	13	[redacted]	3	[redacted]
70-79 yrs	[redacted]	6	[redacted]	5	[redacted]	1	[redacted]
Total	20.2	88*	4.4 (3.5,5.4)	79*	3.9 (3.1,4.9)	22**	1.1 (0.7,1.7)

* Includes 12 – unknown age, ** Includes 2 – unknown age

(data lock 29th March)

OFF-SEN

Benefit calculations: approach

Vaccine effectiveness estimates:

- Against being a **case** (any case, and a long COVID case) = [redacted]
- Against **hospitalisation** = [redacted]
- Against **ICU/HDU admission** = [redacted]
- Against **death** = [redacted]

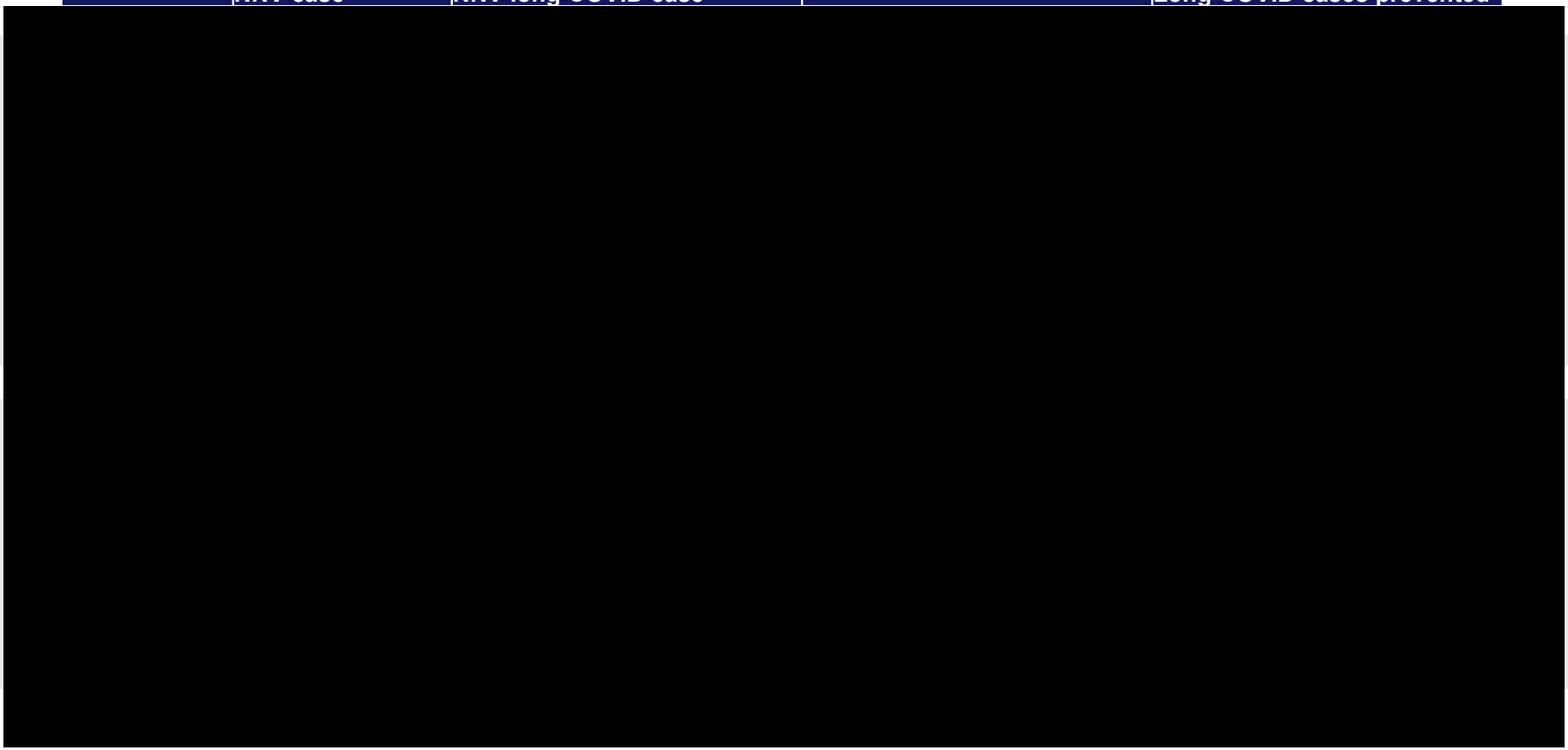
[redacted]

[redacted]

OFF-SEN

Cases and long COVID

	NNV case	NNV long COVID case*		Long COVID cases prevented



Benefits and risks (CVST only, <50 years)

Age group	Hospitalisations prevented (per 1 million doses)	ICU/HDU prevented (per 1 million doses)	Case incidence rate (exc. unlikely per 1 million doses)	Mortality prevented (per 1 million courses)	Fatal incidence rate (inc. unlikely per 1 million doses)
15-19 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20-24 years				[redacted]	
25-29 years	[redacted]	[redacted]		[redacted]	
30-34 years			[redacted]	[redacted]	[redacted]
35-39 years				[redacted]	
40-44 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-49 years				[redacted]	

(data lock 31st March)

Benefits and risks (CVST only, 50+ years)

Age group	Hospitalisations prevented (per 1 million doses)	ICU/HDU prevented (per 1 million doses)	Case incidence rate (per 1 million doses)	Mortality prevented (per 1 million courses)	Fatal incidence rate (per 1 million doses)
50-54 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
55-59 years	[redacted]	[redacted]		[redacted]	
60-64 years			[redacted]	[redacted]	[redacted]
65-69 years	[redacted]	[redacted]		[redacted]	
70-74 years			[redacted]	[redacted]	[redacted]
75-79 years	[redacted]	[redacted]		[redacted]	

(data lock 31st March)

Benefits and risks (CVST + other TE, <50 years)

Age group	Hospitalisations prevented (per 1 million doses)	ICU/HDU prevented (per 1 million doses)	Case incidence rate (exc. unlikely per 1 million doses)	Mortality prevented (per 1 million courses)	Fatal incidence rate (inc. unlikely per 1 million doses)
15-19 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20-24 years				[redacted]	
25-29 years	[redacted]	[redacted]		[redacted]	
30-34 years			[redacted]	[redacted]	[redacted]
35-39 years				[redacted]	
40-44 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-49 years				[redacted]	

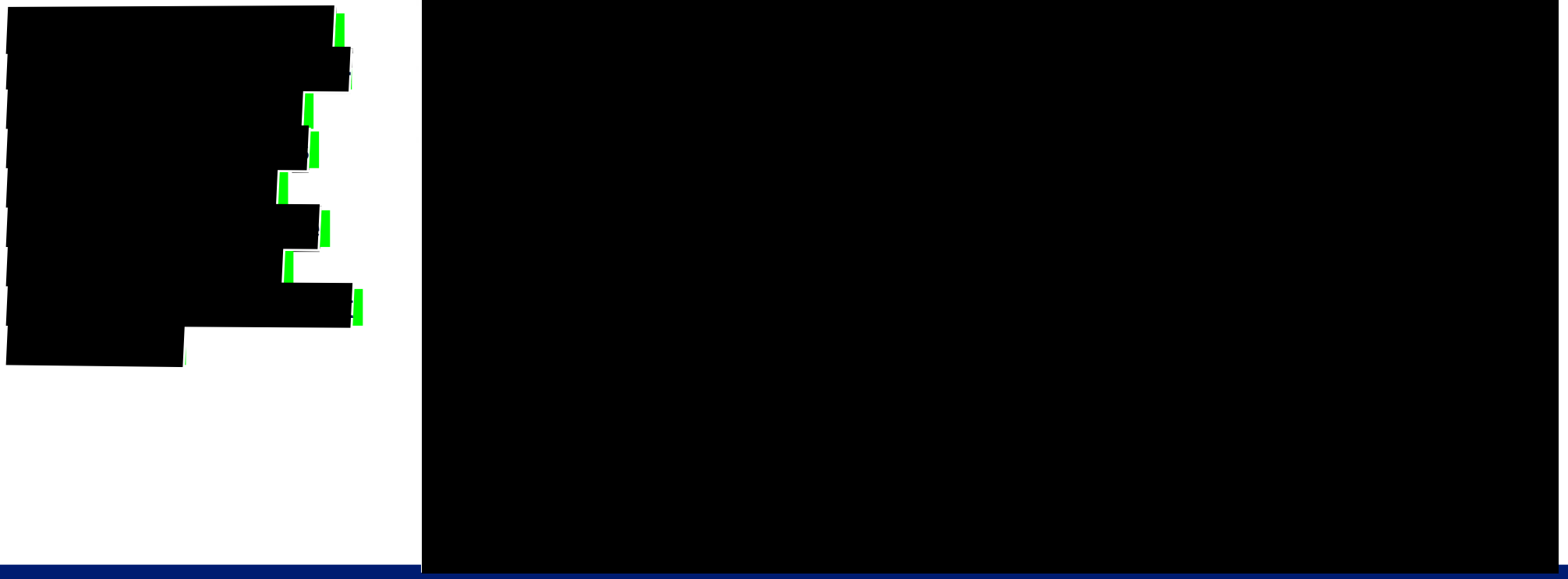
(data lock 31st March)

Benefits and risks (CVST + other TE, 50+ years)

Age group	Hospitalisations prevented (per 1 million doses)	ICU/HDU prevented (per 1 million doses)	Case incidence rate (per 1 million doses)	Mortality prevented (per 1 million courses)	Fatal incidence rate (per 1 million doses)
50-54 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
55-59 years	[redacted]	[redacted]		[redacted]	
60-64 years			[redacted]	[redacted]	[redacted]
65-69 years	[redacted]	[redacted]		[redacted]	
70-74 years			[redacted]	[redacted]	[redacted]
75-79 years	[redacted]	[redacted]		[redacted]	)

(data lock 31st March)

Modelling ([redacted]



MHRA assessment of AstraZeneca's review of global safety data

- Global case picture presented largely reflective of UK experience

- Observed vs. expected
  - TE + thrombocytopenia – increased risk in younger patients
  - For CVST (with/without thrombocytopenia) – increased risk in younger patients
  - For CVST with thrombocytopenia – no age based analyses but overall much higher risk than expected
  - These analyses are limited and include 61 UK cases only (27 CVST + thrombocytopenia)

- Benefit risk assessment uses higher cumulative EU COVID-19 mortality rate (i.e. over 12 months) whereas MHRA analyses uses lower anticipated mortality in a predicted UK third wave

- No additional comments on future epidemiology studies but previous commitment to collaboration

Summary of Proposed Updates to Reg 174 Information for HCPs

New contraindications

Section 4.3 Contraindications

Patients with a history of major venous and arterial thrombosis with thrombocytopenia.

Patients who have experienced such events following vaccination should not receive the second dose of the COVID-19 Vaccine AstraZeneca.

(Based on CHM advice excluding age restriction, sent to AstraZeneca on 5 Apr 2021)

Summary of Proposed Updates to Reg 174 Information for HCPs

New warning

Section 4.4 Special warnings and precautions for use

Thrombocytopenia and coagulation disorders

Serious thromboembolic events with thrombocytopenia, sometimes accompanied by bleeding, have occurred very rarely following vaccination with COVID-19 Vaccine AstraZeneca during post-authorisation use. This includes life-threatening and fatal cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, portal vein thrombosis, as well as arterial thrombosis, combined with thrombocytopenia that can rapidly progress. Multifocal venous and arterial thromboses, have been reported in serious cases. The majority of the events occurred within the first 14 days following vaccination but have also been reported after this period. Risk factors have not been identified. Some cases have increased D-dimer levels >4000ng/mL, positive anti-platelet factor 4 antibodies and laboratory evidence of platelet activation. Based on the available data, a causal relationship has not been established.

(Based on CHM advice excluding age restriction, sent to AstraZeneca on 5 Apr 2021)

Summary of Proposed Updates to Reg 174 Information for HCPs

New warning (continued)

Administration of the COVID-19 Vaccine AstraZeneca in patients with a history of cerebral venous sinus thrombosis, acquired or genetic thrombophilia, heparin-induced thrombocytopenia or antiphospholipid syndrome should be only be considered when the potential benefit outweighs any potential risks.

Healthcare professionals should be alert to the signs and symptoms of thromboembolism and/ or thrombocytopenia. Vaccinated individuals should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg swelling, persistent abdominal pain or unusual skin bruising and or petechia a few days after vaccination. Vaccinated individuals should also seek immediate medical attention if they develop neurological symptoms that start four days or more after vaccination such as new onset or persistent worsening headaches which do not respond to simple painkillers or blurred vision. Patients with thromboembolic events and thrombocytopenia should be urgently referred to a specialist in haematology for advice on further management.

(Based on CHM advice excluding age restriction, sent to AstraZeneca on 5 Apr 2021)

Summary of Proposed Updates to Reg 174 Information for HCPs

Updated warning

Section 4.6 Fertility, pregnancy and lactation

Administration of COVID-19 Vaccine AstraZeneca is not recommended for pregnant women. The thromboembolic events with simultaneous thrombocytopenia described in sections 4.4 and 4.8 are very rare, however pregnancy increases the risk of thrombosis and thrombocytopenia may occur in the last trimester. Although evidence is very limited, this population is potentially at further risk of such events following vaccination.

(Based on CHM advice excluding age restriction, sent to AstraZeneca on 5 Apr 2021)

Summary of Proposed Updates to Reg 174 Information for HCPs

New listing of thromboembolic events with thrombocytopenia

Section 4.8

Very rare events of major venous and arterial thrombosis with thrombocytopenia, sometimes accompanied with bleeding, have also been reported following vaccination with COVID-19 Vaccine AstraZeneca. A causal relationship has not been established (see section 4.4).

(Based on CHM advice excluding age restriction, sent to AstraZeneca on 5 Apr 2021)