Update on COVID-19 vaccines and risk of thromboembolic events with concurrent thrombocytopenia

EWG 26th April 2021(data lock: 21st April 2021 [AZ COVID-19 vaccine])

Medicines & Healthcare products Regulatory Agency

OFFICIAL-SENSITIVE

Background

Ongoing, detailed review of reports of very rare events of thromboembolic events (including CVST and non-CVST events) with concurrent thrombocytopenia associated with Covid-19 vaccines.

Assessment of Yellow Card Scheme reports against a case definition developed with independent expert advice. Foreign cases were considered for the Pfizer, Moderna and Janssen vaccines.

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

- VBR EWG meetings: 27 & 31 March; 6, 12 & 19 April 2021
- CHM meetings: 1, 4, 6 & 8 April 2021

AZ Vaccine: summary of EMA regulatory actions

Article 5(3) of Regulation (EC) No. 726/2004 Referral for AZ COVID-19 Vaccine

- News 23 April 2021

  Interim Opinion of the CHMP pursuant to Article 5(3) for Vaxzevria 23 Apr 2021
  - provided analyses of benefits for different age groups & varying infection rates for use by national authorities in planning vaccine rollout programmes;
  - insufficient data for risk estimates by gender;
  - unusual blood clots & low platelets: estimated incidence 1 in 100,000 vaccinated people;
  - benefit-risk balance remains positive for all adults in all age groups;
  - 2nd dose: inadequate data to determine if risk differs from 1st dose;
  - no regulatory action.
  - Annex to Vaxzevria Art.5.3 - Visual risk contextualisation (europa.eu)

AZ vaccine: publications

Greinacher 2021 Anti-SARS-CoV-2 spike protein and anti-platelet factor 4 antibody responses induced by COVID-19 disease and ChAdOx1 nCov-19 vaccination PREPRINT

- Compared immunogenic epitopes of human PF4 & SARS-CoV-2 spike protein using prediction tools & 3D modelling software:
  - Identified 3 motifs (>10 amino acids long) within spike protein that shared an epitope with PF4;
- sera from 222 PCR-confirmed Covid-19 registry patients tested for PF4/heparin ELISA, heparin-dependent & PF4-dependent platelet activation assays:
  - 19 (8.6%) Covid-19 patient sera positive in the PF4/heparin ELISA without platelet activation:
- Immunogenic reactivity of purified anti-PF4 & anti-PF4/heparin antibodies from 6 patients with vaccine-induced thrombotic TCP (VITT) tested against recombinant SAR-CoV-2 spike protein:
  - Purified anti-PF4 and anti-PF4/heparin antibodies from 2 VITT patients did not show cross-reactivity to SARS-CoV-2 spike protein.
- Unlikely that the intended vaccine-induced immune response against SARS-Cov-2 spike protein would induce VITT.

AZ vaccine: publications

Greinacher 2021. Towards understanding ChAdOx1 nCov-19 vaccine-induced immune thrombotic thrombocytopenia (VITT) PREPRINT

- Biophysical interactions between AZ COVID-19 vaccine, PF4 and anti-PF4 antibody (from patients with VITT) were explored visually using dynamic light scattering, 3D-super-resolution and electron microscopy;
- AZ COVID-19 vaccine and PF4 compositions were analysed using mass spectrometry/NMR:
- Post-vaccine inflammatory reactions were analysed;
- Evaluated ability of VITT antibodies to release DNA-containing neutrophil extracellular traps (NETs);
- Measured DNase activity in VITT patient sera using single radial enzyme diffusion assay;

Concluded:

  - AZ COVID-19 vaccine constituents form antigenic complexes with PF4;
  - EDTA increases microvascular permeability in mice;
  - Anti-PF4 Abs may be caused by a proinflammatory reaction to vaccine Ag;
  - PF4 enhanced VITT Ab-driven NETs formation & DNase activity was reduced in VITT sera;
  - VITT triggered by adenovirus +/- other PF4-DNA interactions. Proinflammatory response induced by vaccine components could be reduced by omitting EDTA & impurities.

- MHRA Quality: unpublished, speculative and unproven. We have data about levels of HLA in a few batches that may prove useful.

AZ vaccine: publications - case reports

Blauenfeldt 2021. Thrombocytopenia with acute ischemic stroke and bleeding in a patient newly vaccinated with an adenoviral vector-based COVID-19 vaccine. Journal of Thrombosis and Haemostasis.

Muster 2021. Pulmonary embolism and thrombocytopenia following ChAdOx1 vaccination. Lancet. 'Similar to HIT,' PF4 Abs negative (assay not specified, no modified platelet activation test). Responded to supratherapeutic dose of LMWH and dexamethasone.

Mehta 2021. CVST and thrombocytopenia after COVID-19 vaccintation - A report of two UK cases. Brain Behaviour and Immunity

Castelli 2021 CVST associated with thrombocytopenia post-vaccination for COVID-19. Critical Care

No new proposed causal mechanisms.

AZ Covid-19 Vaccine: summary of case reports

209 UK cases of thromboembolic events with thrombocytopenia including confirmed, probable or possible cases (120 female, 89 male):

- **84 CVST** (mean age 46.5 years; range 18-85 years [n=81], 21 fatal [25%])
- **123 non-CVST** (mean age 54.7 years; range 21-93 years [n=115], 20 fatal [16%])
- **2 unclear** ([redacted])

Case definition		Number of cases	Number of fatalities
Confirmed	Probable + PF4 antibodies	49	13
Probable	Possible + D-dimer >4000 mcg/L	74	10
Possible	Venous/arterial thrombosis + TCP	86	18
	Totals	209	41
	Overall case fatality rate	**20 %**	

(Previous DLP 14 Apr 2021: overall 168 cases; 35 confirmed; 69 probable; 64 possible; 32 fatalities).

(data lock 21 April 2021)

AZ Covid-19 vaccine: summary of 14 cases reported after 2nd dose (fatal)

Case No.	Age, Sex	TTO (days)	Events	Co-morbidities	Medication	PF 4 Antibodies ELISA test
Possible cases						
[redacted]	[redacted]	[redacted]	[redacted] D-dimer UNK	[redacted]	None	UNK
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probable case						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	None	[redacted]

[redacted]; pl=platelet count (x10^9/L); [redacted] UNK=result unknown.

Plus: unlikely, 7 cases; criteria not met, 3 cases. PF 4 antibody test - negative in 1; not done/UNK in 9.

AZ COVID-19 vaccine: outcomes – CVST, confirmed cases (fatal)

Case No.	Age,	Maximal deficit, surgical treatment	Co-morbidities	Outcome
[redacted]	[redacted]	[redacted]	None	Not recovered
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	**None**	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	None	[redacted]
[redacted]	[redacted]	[redacted]	**None**	[redacted]
[redacted]				

AZ COVID-19 vaccine: outcomes – CVST + non-CVST, confirmed cases (fatal)

Case No.	Age,	Maximal deficit, surgical treatment	Co-morbidities	Outcome
[redacted]	[redacted]	[redacted]	None	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted];				

Plus 1 confirmed patient with unknown site of thrombosis

AZ COVID-19 vaccine: outcomes – non-CVST, confirmed cases (fatal)

Case No.	Age,	Maximal deficit, surgical treatment	Co-morbidities	Outcome
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	None	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	None	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	None	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	None	[redacted]
[redacted]				

AZ COVID-19 vaccine: outcomes – non-CVST, confirmed cases (fatal)

Case No.	Age,	Maximal deficit, surgical treatment	Co-morbidities	Outcome
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	None	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	None	[redacted]
[redacted]	[redacted]	[redacted]	None	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	None	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	None	[redacted]
[redacted]	[redacted]	DVT	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				

Pfizer Vaccine: summary of case reports

- One probable and one possible UK cases:
  - Possible: [redacted]
  - Probable: [redacted]
- No change to non-UK data - 5 cases including confirmed, probable or possible cases:
  - 1 CVST ([redacted] (20%))

Case definition		Number of cases	Number of fatalities
Confirmed	Probable + PF4 antibodies	0	0
Probable	Possible + D-dimer >4000 mcg/L	1	1
Possible	Venous/arterial thrombosis + TCP	4	1
	Totals	5	2
	Overall case fatality rate	**40%**	

(data lock 21 April 2021)

Moderna: summary of case reports

No UK cases of thromboembolic events with thrombocytopenia

No change in the non-UK reports:

- One non-UK case borderline for meeting the possible case definition
  - [redacted]
  - [redacted]
  - [redacted]
- One unlikely non-UK case of [redacted] patient with [redacted] and [redacted]

(data lock 14 April 2021)

- Janssen Vaccine: EMA update of product information

20 April EMA concluded a warning should be added on thromboses with thrombocytopenia with the Janssen vaccine

- Benefit risk remains positive
- Added as a very rare side effect in 4.8
- DHPC planned

Based on same 9 cases previously identified; 7.7 million doses used in US as of 15 April

EWG recently considered UK CMA application, and this will go to CHM

Janssen Vaccine: summary of case reports

- Janssen vaccine in use in US with > 7.7 million doses administered of 15 April
- 9 non-UK cases including confirmed, probable and possible cases from both clinical trial and post-authorisation use:
  - 6 CVST (1 male, 5 female, mean age 31.6 years; range 18-48 years), 1 fatal
  - 3 non-CVST (2 male, 1 female, mean age 64.6 years; range 59-72 years), none fatal

Case definition		Number of cases	Number of fatalities
Confirmed	Probable + PF4 antibodies	1	0
Probable	Possible + D-dimer >4000 mcg/L	0	0
Possible	Venous/arterial thrombosis + TCP	8	1
	Totals	9	1
	Overall case fatality rate	**11%**	

US usage estimated 66.5.% 18-59 -years and 33.5% ≥60-years

(data lock 12 Apr 2021)

FDA & CDC lift recommended pause on Janssen COVID-19 vaccine use following thorough safety review 23 Apr 2021

Thorough review of spontaneous reports, medical literature and information from global regulatory partners.

A total of 15 cases of thrombosis-thrombocytopenia syndrome were identified:

- All female;
- Median age 37 years (range: 18 – 59 years);
- Symptom onset: 6 – 15 days after vaccination.

US exposure >6.8 million doses of Janssen vaccine on 13 Apr 2021.

Monitoring for safety will continue

Estimated exposure data – AZ 1st & 2nd doses

Age group	Estimated number of first AZ doses in UK (1,000,000s)	%
18-29 years	[redacted]	[redacted]
30-39 years	[redacted]	[redacted]
40-49 years	[redacted]	[redacted]
50-59 years	[redacted]	[redacted]
60-69 years	[redacted]	[redacted]
70-79 years	[redacted]	[redacted]
80+ years	[redacted]	[redacted]
Total	22.0	100

Age group	Estimated number of second AZ doses in UK (1,000,000s)	%
18-29 years	[redacted]	[redacted]
30-39 years	[redacted]	[redacted]
40-49 years	[redacted]	[redacted]
50-59 years	[redacted]	[redacted]
60-69 years	[redacted]	[redacted]
70-79 years	[redacted]	[redacted]
80+ years	[redacted]	[redacted]
Total	4.4	100

(data lock 21 April 2021)

Incidence rate – CVST (first/unknown dose)

Age group	Estimated number of first doses in UK (1,000,000s)	Total number of cases (exc. unlikely cases)	Case incidence rate (per 1 million doses)	Number of fatal cases (exc. unlikely)	Fatal incidence rate (per 1 million doses)
18-29 yrs	[redacted]	17	[redacted]	5	[redacted]
30-39 yrs	[redacted]	10	[redacted]	5	[redacted]
40-49 yrs	[redacted]	14	[redacted]	2	[redacted]
50-59 yrs	[redacted]	26	[redacted]	7	[redacted]
60-69 yrs	[redacted]	11	[redacted]	2	[redacted]
70-79 yrs	[redacted]	2	[redacted]	0	[redacted]
80+ yrs	[redacted]	1	[redacted]	0	[redacted]
Total	22.0	84*	3.8 (3.0,4.7)	21**	1.0 (0.6,1.5)

(data lock 21 April 2021)

* Includes 3 unknown age, 2 unknown dose
** Includes 1 unknown dose

Incidence rate – CVST (first/unknown dose) – 5 years

Age group	Estimated number of first doses in UK (1,000,000s)	Total number of cases (exc. unlikely cases)	Case incidence rate (per 1 million doses)	Number of fatal cases (exc. unlikely)	Fatal incidence rate (per 1 million doses)
15-19 yrs	[redacted]	2	[redacted])	1	[redacted])
20-24 yrs	[redacted]	5	[redacted])	2	[redacted])
25-29 yrs	[redacted]	10	[redacted])	2	[redacted])
30-34 yrs	[redacted]	9	[redacted])	5	[redacted])
35-39 yrs	[redacted]	1	[redacted])	0	[redacted]
40-44 yrs	[redacted]	1	[redacted])	0	[redacted])
45-49 yrs	2.1	13	6.1 (3.2,10.4)	2	0.9 (0.1,3.4)

(data lock 21 April 2021)

Incidence rate – CVST + other TE (first/unknown dose)

Age group	Estimated number of first doses in UK (1,000,000s)	Total number of cases (exc. unlikely cases)	Case incidence rate (per 1 million doses)	Number of fatal cases (exc. unlikely)	Fatal incidence rate (per 1 million doses)
18-29 yrs	[redacted]	24	[redacted])	6	[redacted])
30-39 yrs	[redacted]	28	[redacted])	8	[redacted])
40-49 yrs	[redacted]	30	[redacted])	4	[redacted])
50-59 yrs	[redacted]	59	[redacted])	12	[redacted])
60-69 yrs	[redacted]	31	[redacted])	6	[redacted])
70-79 yrs	[redacted]	18	[redacted])	2	[redacted]
80+ yrs	[redacted]	4	[redacted])	2	[redacted])
Total	22.0	205*	9.3 (8.1,10.7)	40**	1.8 (1.3,2.5)

(data lock 21 April 2021)

* Includes 11 unknown age, 9 unknown dose
** Includes 4 unknown dose

Incidence rate – CVST + other TE (first/unknown dose) – 5 years

Age group	Estimated number of first doses in UK (1,000,000s)	Total number of cases (exc. unlikely cases)	Case incidence rate (per 1 million doses)	Number of fatal cases (exc. unlikely)	Fatal incidence rate (per 1 million doses)
15-19 yrs	[redacted]	2	[redacted])	1	[redacted])
20-24 yrs	[redacted]	10	[redacted])	3	[redacted])
25-29 yrs	[redacted]	12	[redacted])	2	[redacted])
30-34 yrs	[redacted]	15	[redacted])	6	[redacted])
35-39 yrs	[redacted]	13	[redacted])	2	[redacted])
40-44 yrs	[redacted]	3	[redacted])	1	[redacted])
45-49 yrs	[redacted]	27	[redacted])	3	[redacted])

(data lock 21 April 2021)

Comments on incidence rates

- Only a small increase in number of first doses – deployment currently focused on 2nd doses
- CVST rate (1st/unknown dose) - Incidence rate: 3.6 (last EWG DLP) – 3.8 (current DLP)
  - Only v small change in fatal case rate (1 new fatal CVST)
- CVST + other TE (1st/unknown dose) - Incidence rate: 7.9 (last EWG DLP) – 9.3 (current DLP)
  - Confidence intervals overlap but continuation of increasing trend – likely better ascertainment and roll out to younger patients
  - No new cases in ages 18-29 years
  - 7 new cases in 30-39 years - Incidence rate: 12.8 (last EWG DLP) – 16.4 (current DLP)
  - Larger numbers of cases in 40-49 and 50-59 years in line with current / recent deployment – smaller impact on incidence rate
  - Only small change in fatal case rate - Incidence rate: 1.5 (last EWG DLP) – 1.8 (current DLP)
- 4.4 million 2nd AZ doses – Incidence rate: 0.4 (0.01,2.4; last EWG DLP) - 0.9 (0.2,2.3; current)
- Expected trend towards increased reporting of non-CVST cases and non-fatal outcomes

(data lock 21 April 2021)

Incidence rate - by sex

- **CVST**

Age group	Sex	Estimated number of first doses of AZ (1,000,000s)	Number of cases determined to be confirmed/probable/possible	Case incidence rate (per 1 million doses)
<50 years	Male	[redacted]	15	[redacted]
	Female	[redacted]	26	[redacted])
Overall	Male	[redacted]	33	[redacted])
	Female	[redacted]	51	[redacted])

- **CVST + other TE**

Age group	Sex	Estimated number of first doses of AZ (1,000,000s)	Number of cases determined to be confirmed/probable/possible	Case incidence rate (per 1 million doses)
<50 years	Male	[redacted]	34	[redacted])
	Female	[redacted]	48	[redacted])
Overall	Male	[redacted]	88	[redacted])
	Female	[redacted]	117	[redacted])

OFF-SEN

Benefit calculations: approach

Vaccine effectiveness estimates:

- Against being a **case** (any case, and a long COVID case) = 60% (single dose)
- Against **hospitalisation** = 80% (single dose)
- Against **ICU/HDU admission** = 80% (single dose)
- Against **death** = 80% at first dose, 96% at second dose i.e. an additional 16% at second dose

Number needed to vaccinate calculated for England is based on infection, hospitalisation and death rates from the second wave only – (week 50 2020-end of week 12 2021). For currently unvaccinated groups this therefore assumes a future wave of a similar size and severity in these groups.

Hospitalisation/ICU estimates based on aggregate data from the SARI Watch surveillance system from 135 acute trusts

Benefits and risks (CVST only, <50 years)

<table>
<tr><th>Age group</th><th>Hospitalisations prevented (per 1 million doses)</th><th>ICU/HDU prevented (per 1 million doses)</th><th>Case incidence rate (per 1 million doses)</th><th>Mortality prevented (per 1 million courses)</th><th>Fatal incidence rate (per 1 million doses)</th></tr>
<tr><td>15-19 years</td><td rowspan="2">325</td><td rowspan="2">19</td><td rowspan="3">14.1 (8.2,22.6)</td><td>4</td><td rowspan="3">4.2 (1.3,9.7)</td></tr>
<tr><td>20-24 years</td><td>8</td></tr>
<tr><td>25-29 years</td><td rowspan="4">857</td><td rowspan="4">85</td><td>13</td></tr>
<tr><td>30-34 years</td><td rowspan="2">5.9 (2.8,10.8)</td><td>29</td><td rowspan="2">2.9 (1.0,6.8)</td></tr>
<tr><td>35-39 years</td><td>53</td></tr>
<tr><td>40-44 years</td><td rowspan="2">4.0 (2.2,6.7)</td><td>80</td><td rowspan="2">0.6 (0.07,2.1)</td></tr>
<tr><td>45-49 years</td><td>1,464</td><td>193</td><td>158</td></tr>
</table>

(data lock 21 April 2021)

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	1,893	237	4.0 (2.6,5.9)	261	1.1 (0.4,2.2)
55-59 years	2,920	402		441	
60-64 years			2.3 (1.2,4.1)	624	0.4 (0.05,1.5)
65-69 years	3,997	378		1,415	
70-74 years			0.6 (0.07,2.2)	1,890	0 (0,1.1)
75-79 years	8,548	231		3,667	
80+ years*			0.9 (0.02,5.0)	6,506	0 (0,3.3)

* To note benefit estimates are for the 80-84 age cohort only

(data lock 21 April 2021)

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)
15-19 years	325	19	20.0 (12.8,29.7)	4	5.0 (1.8,10.9)
20-24 years				8	
25-29 years	857	85		13	
30-34 years			16.4 (10.9,23.7)	29	4.7 (2.0,9.2)
35-39 years				53	
40-44 years			8.6 (5.8,12.3)	80	1.2 (0.3,2.9)
45-49 years	1,464	193		158	

(data lock 21 April 2021)

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	1,893	237	9.1 (7.0,11.8)	261	1.9 (1.0,3.2)
55-59 years	2,920	402		441	
60-64 years			6.5 (4.4,9.2)	624	1.3 (0.5,2.7)
65-69 years	3,997	378		1,415	
70-74 years			5.5 (3.3,8.7)	1,890	0.6 (0.1,2.2)
75-79 years	8,548	231		3,667	
80+ years			3.4 (1.0,9.2)	6,506	1.8 (0.2,6.5)

* To note benefit estimates are for the 80-84 age cohort only

(data lock 21 April 2021)

Questions to the EWG

Having considered the evidence presented, the EWG is asked to advise on the following questions:

- Based on the evidence presented does the EWG consider the benefit:risk remains favourable for all patients and for specific age groups?
- Does the EWG consider there might be an increased risk for the second dose of the vaccine?
- Does the EWG consider there is need for action with regards to the Pfizer, Moderna or Janssen vaccines in relation to this potential risk?