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

EWG 19th April 2021(data lock: 14th April 2021 [AZ COVID-19 vaccine])

Medicines & Healthcare products Regulatory Agency

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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 and Moderna vaccines.

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

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

AZ Vaccine: summary of recent MHRA regulatory action

15 Apr 2021: updated product information published

- Information for Healthcare Professionals on COVID-19 Vaccine AstraZeneca

  Section 4.3 includes 2 contraindications:

  – Patients with a history of heparin-induced thrombocytopenia and thrombosis (HITT or HIT type 2).

  – Patients who have experienced major venous and/or arterial thrombosis occurring with thrombocytopenia following vaccination with any COVID-19 vaccine should not receive a second dose of COVID-19 Vaccine AstraZeneca.

  Section 4.4 includes a warning on use in those with previous CVST or APLS

- Information for UK recipients on COVID-19 Vaccine AstraZeneca

  Section 2 advice is aligned to PHE with risk period from around 4 days after vaccination

AZ Vaccine: summary of EMA regulatory actions

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

- Triggered by the EC on 14 April 2021. It has requested a further analysis of data including:
  - Vaccine exposure data stratified by age/gender in member states;
  - Disease epidemiology including infection rates, hospitalisations, morbidity & mortality to better characterise the benefit-risk profile of the vaccine in different age groups &/or genders;
  - Identification of possible risk factors;
  - Provide a recommendation on the administration of the second dose;

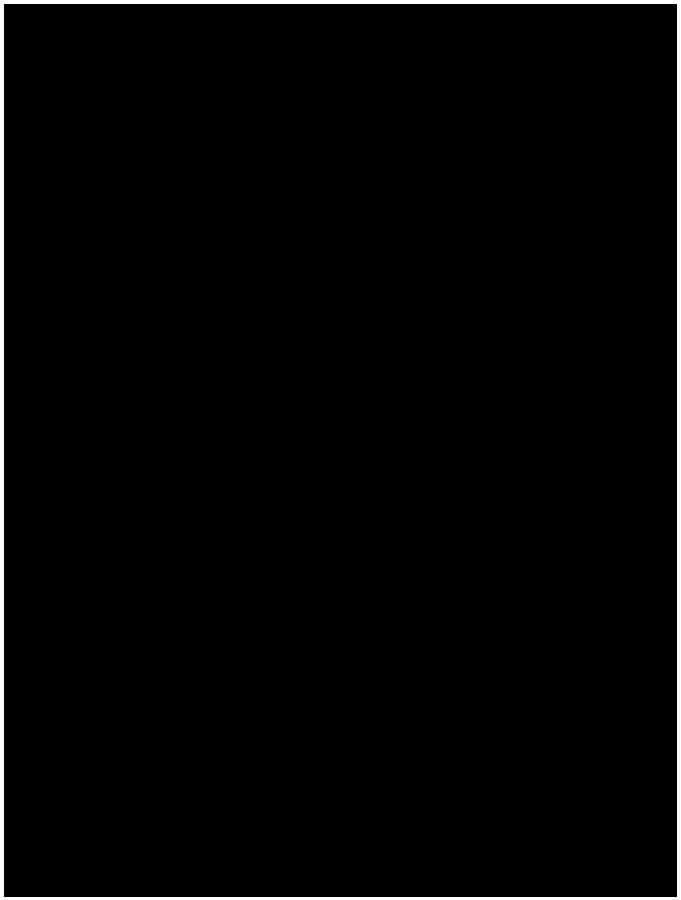
  Interim recommendations requested by 22 Apr 2021.
- PRAC Signal Assessment Report on embolic & thrombotic events with AZ COVID-19 Vaccine

Publications

Oldenburg 2021 Diagnosis and management of vaccine-related thrombosis following AZ COVID-19 vaccination: guidance statement from the GTH

- Patients with a history of thrombosis and/or thrombophilia not at increased risk;
- Investigations if TCP and/or thrombosis:
  - PF4/heparin Abs using sensitive tests:
    - HYPHEN BioMed ZYMUTEST EIA;
    - Immucor GTI Diagnostics EIA;
  - Platelet activation tests if PF4 Ab positive:
    - HIPA/SRA assay
    - If HIPA/SRA negative, modified HIPA assay*
- IVIG can cause false-negative test results;
- Always consider alternative causes, irrespective of VIPIT/HIT test results.

*PF4-enhanced platelet activation test (Greinacher 2021)



Publications

Schultz 2021 Thrombosis & thrombocytopenia after ChAdOx1 nCoV-19 Vaccination (NEJM)

- Norwegian case series (Norwegian AZ COVID-19 D1 vaccine exposure: 132,686 people):
  - 5 HCPs (4 female, 32 to 54 years, TTO 7 to 10 days; 3 fatal);
  - 4 CVST with intracranial haemorrhage, 1 splanchnic/azygos venous thromboses;
  - 1 had APL Abs (slightly elevated anticardiolipin IgG Ab level); 2 on hormonal contraception & 1 on HRT;
  - Lowest platelet counts: 14 to 70 $x10^9$/L, peak D-dimers: 13 to >35 mg/L
  - All 5 had high levels of PF4-polyanion complex IgG Abs (ODs 2.9 to 3.8, 4 had received LMWH before sampling), 4 activated platelets in absence of heparin & platelet aggregation inhibited by high-dose heparin in 4 (efficiently in 2, less efficiently in 2)
  - None had SARS-CoV-2 nucleocapsid protein Abs
- No mechanism proposed

Publications

Greinacher 2021 Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination (NEJM)

- Case series updated:
  - 11 cases (9 female, 22 to 49 years, platelet counts 9 to 107 $x10^9$/L; TTO 5 to 16 days;
  - 5 DIC; 6 fatal; 9 PF4 Ab positive with PF4-dependent platelet activation)
  - 1 patient had previous von Willebrand disease, ACL Abs & factor V Leiden.
- 24 samples from other patients with suspected vaccine-associated thrombotic events showed strong reactivity in screening PF4-heparin ELISA; 22 of these had PF4-dependent platelet activation & 19 were inhibited by low-dose low-molecular weight heparin & 27 were inhibited by high-dose heparin;
- 1 possible trigger of PF4-reactive Abs could be free DNA in the vaccine;
- Potential diagnostic & treatment strategies outlined.

Publications

Bayas 2021 Bilateral superior ophthalmic vein thrombosis, ischaemic stroke, and immune thrombocytopenia after ChAdOx1 nCoV-19 vaccination (Lancet)

- Case report: 55 German female, TTO 7 days after 1st dose of AZ COVID-19 vaccine
  - 3 days flu-like symptoms then conjunctival congestion, diplopia, eye pain, visual acuities 0.85;
  - no significant medical history & non-smoker;
- Investigations:
  - MRI: bilateral superior ophthalmic vein thromboses with high T2 signal intensity;
  - isolated thrombocytopenia with platelet count 30 $x10^9$/L;
  - antiplatelet Abs: IgG positive, IgM borderline;
  - platelet suspension immunofluorescence test & mAb-specific immobilisation of platelet antigens assay were positive supporting a diagnosis of **secondary immune TCP;**
  - other causes excluded (APLS, TMA, HBV, HCV, HIV, CMV, hantavirus, *H.pylori*);
  - PF4 Abs negative using lateral flow immunoassay;
- Treatment: dexamethasone 40mg daily for 4 days + heparin, platelet count increased to approx. 80:
- 8 days later, ischaemic stroke with aphasia, hemiparesis and focal seizures, switched to phenprocoumon & later discharged.

Publications:

Scully et al. 2021 Pathologic antibodies to PF4 after ChAdOx1 nCoV-19 Vaccination

- In the absence of previous prothrombotic medical conditions, 22 patients presented with acute thrombocytopenia and thrombosis, primarily cerebral venous thrombosis, and 1 patient presented with isolated thrombocytopenia and a haemorrhagic phenotype;
- All had negative SARS-CoV-2 PCR assay at presentation:
- All the patients had low or normal fibrinogen levels and elevated d-dimer levels at presentation.
- No evidence of thrombophilia or causative precipitants was identified;
- Testing for antibodies to platelet factor 4 (PF4) was positive in 22 patients (with 1 equivocal result) and negative in 1 patient.
- An investigation & management algorithm is proposed.

AZ Covid-19 Vaccine: summary of case reports

168 UK cases of thromboembolic events with thrombocytopenia including confirmed, probable or possible cases (96 female, 75 male):

- **77 CVST** (mean age 47 years; range 18-85 years [n=74), 19 fatal (25%)
- **91 non-CVST** (mean age 54 years; range 21-93 years [n=83]), 13 fatal (14%)

Case definition		Number of cases	Number of fatalities
Confirmed	Probable + PF4 antibodies	35	10
Probable	Possible + D-dimer >4000 mcg/L	69	9
Possible	Venous/arterial thrombosis + TCP	64	13
	Totals	168	32
	Overall case fatality rate	**19 %**	

(data lock 14 April 2021)

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

Case No.	Age, Sex	TTO (days)	Events	Co-morbidities	Medication
Unlikely cases					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Unknown
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Unknown
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probable case					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted] pl=platelet count (x10^9/L); [redacted]

(data lock 14 April 2021)

Pfizer Vaccine: summary of case reports

- One possible UK case: [redacted].
  3 UK "unlikely" cases of thromboembolic events with thrombocytopenia - confounding factors and not meeting case definition criteria
- 5 non-UK cases including confirmed, probable or possible cases:
  - 1 CVST ([redacted]-year-old [redacted] (20%))
  - 4 non-CVST (mean age 62 years; range 53-84 years [n=4]), 1 fatal)

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 14 April 2021)

Moderna: summary of case reports

No UK cases of thromboembolic events with thrombocytopenia

No significant 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] – [redacted] patient with [redacted].

(data lock 14 April 2021)

Joint CDC & FDA Statement on Janssen COVID-19 Vaccine

- 13 April 2021, FDA suspended use of the Janssen COVID-19 Vaccine and announced a planned analysis of US cases of CVST occurring with thrombocytopenia;
- 6 female cases, aged 18 to 48 years with symptoms developing 6 to 13 days after vaccination, 1 fatal;
- > 6.8 million doses of the Janssen vaccine administered;
- 'In this setting, administration of heparin may be dangerous, and alternative treatments need to be given'
- People developing severe headache, abdominal pain, leg pain, or shortness of breath within three weeks after vaccination should contact their health care provider.

Janssen COVID-19 vaccine and CVST with thrombocytopenia - Update for clinicians on early detection and treatment CDC15 Apr 2021

J&J have also delayed the roll out in the EU and paused dosing of the vaccine in clinical trials to update the investigator/participant and information

Janssen Vaccine: summary of case reports

- Janssen vaccine in use in US with > 6.8 million doses administered of 12 April; roll out in EU now delayed
- 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)

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	21.2	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	2.3	100

(data lock 14 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])	3	[redacted])
30-39 yrs	[redacted]	9	[redacted])	4	[redacted]
40-49 yrs	[redacted]	9	[redacted])	1	[redacted])
50-59 yrs	[redacted]	23	[redacted])	7	[redacted])
60-69 yrs	[redacted]	13	[redacted])	4	[redacted]
70-79 yrs	[redacted]	2	[redacted]	0	[redacted])
80+ yrs	[redacted]	1	[redacted])	0	[redacted])
Total	21.2	77*	3.6 (2.9,4.5)	19**	0.9 (0.5,1.4)

(data lock 14 April 2021)

* Includes 3 unknown age, 6 unknown dose
** Includes 4 unknown dose

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]	4	[redacted]
30-39 yrs	[redacted]	21	[redacted]	7	[redacted]
40-49 yrs	[redacted]	20	[redacted]	2	[redacted]
50-59 yrs	[redacted]	48	[redacted]	11	[redacted]
60-69 yrs	[redacted]	25	[redacted]	4	[redacted]
70-79 yrs	[redacted]	14	[redacted]	2	[redacted]
80+ yrs	[redacted]	5	[redacted]	2	[redacted]
Total	21.2	168*	7.9 (6.8,9.2)	32**	1.5 (1.0,2.1)

(data lock 14 April 2021)

* Includes 11 unknown age, 13 unknown dose
** Includes 4 unknown dose

Comments on incidence rates

- Only a small increase in number of first doses – deployment currently focused on 2nd doses
- 2.3 million 2nd AZ doses – incidence rate 0.4 (0.01,2.4)
- CVST rate – Incidence rate: 2.4 (last EWG DLP) – 3.6 (current DLP)
- CIs overlap, no change in fatal case rate
  - Largest number of cases 50-59 years (+ 9 cases, 2.2 -> 4.8)
  - Largest impact on rate 18-29 years (+ 8 cases, 7.7 -> 14.0)
- CVST + other TE – Incidence rate: 4.9 (last EWG DLP) – 8.0 (current DLP)
  - Significant increase since last DLP, only small change in fatal case rate
  - Largest number of cases 50-59 years (+ 22 cases, 4.1 -> 7.4)
  - Largest impact on rate 18-29 years (+12 cases, 10.2 -> 19.8)
  - Also, notable increases in those age 70+ years
- Expected trend towards increased reporting of non-CVST cases and non-fatal outcomes

(data lock 14 April 2021)

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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)

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	14.0 (8.2,22.5)	4	2.5 (0.5,7.2)
20-24 years				8	
25-29 years	857	85		13	
30-34 years			5.5 (2.5,10.5)	29	2.5 (0.7,6.3)
35-39 years				53	
40-44 years			3.4 (1.6,6.5)	80	0.4 (0.01,2.1)
45-49 years	1,464	193		158	

(data lock 14 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	4.8 (3.0,7.2)	261	1.1 (0.4,2.2)
55-59 years	2,920	402		441	
60-64 years			2.7 (1.4,4.6)	624	0.8 (0.2,2.1)
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*			0.8 (0.02,4.9)	6,506	0 (0,3.3)

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

(data lock 14 April 2021)

Benefits and risks (CVST + other TE, <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>
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(data lock 14 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)
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(data lock 14 April 2021)

ADR reports: proposed triggers for regulatory action including urgent actions

- significant changes in the overall incidence rates or in those for individual age-groups;
- significant changes in overall benefit-risk or for individual age groups for the current safety issue (blood clots with thrombocytopenia);
- significant cluster of serious events under current case definition/fatal incidents;
- decision by another regulator to limit or suspend use;
- recommendation from manufacturer to limit or suspend use;
- publication of new research that indicates urgent action may be required;
- other issues that in the opinion of the MHRA and chair of the EWG/CHM warrant urgent discussion.

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?