Public Health England

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Event	**Update on National incident in response to reports of thrombosis with thrombocytopenia following vaccination with the COVID-19 AstraZeneca vaccine**
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PHE NIERP Level	**National standard response**
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Background and Interpretation:

This briefing note is an update to the briefing note issued on the 19th April 2021 relating to the national incident response to reports of thrombosis with thrombocytopaenia following the AstraZeneca (AZ) COVID-19 vaccine. Since the 4th January to 28th April 2021, 22.6 million first doses and 5.9 million second doses of the AZ vaccine have been administered across the UK (1). The COVID-19 vaccine programme in England has been estimated to have prevented 10,400 deaths in adults aged 60 years and older till the end of March (2) with a vaccine effectiveness of a single dose against hospitalisation estimated at 80% for both the Pfizer/BioNTech and the AZ vaccines (3).

Based on reporting through the MHRA Yellow Card Scheme, as of 28th April 2021, there have been 242 suspected cases of thromboembolic events occurring with thrombocytopenia across the UK following AZ vaccination, giving an overall incidence of 10.5 cases per million first doses (1). To date, no confirmed cases have occurred after the second dose of AZ vaccine. Of the suspected cases, 93 reports are of a very rare and specific type of syndrome of blood clots in the cerebral veins, known as cerebral venous sinus thromboses (CVST) occurring together with low platelet counts. This syndrome has affected patients of all ages and genders, although there does appear to be a trend towards an increased incidence in younger adult age groups. The cases are unusual because despite thrombocytopenia, there is progressive thrombosis, primarily venous, including CVST and portal vein thrombosis, as well as the more usual presentations of deep vein thrombosis and pulmonary embolism. Arterial events have also been reported. Antibodies to platelet factor 4 (PF4) have been identified and so this syndrome appears to have similarities to heparin-induced thrombocytopenia (HIT), but in the absence of patient exposure to heparin treatment. Early recognition and appropriate treatment with Intravenous Immunoglobulin (IVIG) and the avoidance of platelet transfusions appear to improve outcomes, with current case fatality rates estimated at 20%.

Investigations are underway to understand the biological mechanisms and whether this is related to the vaccine platform (the way in which the vaccine delivers antigen) or some other immunological mechanism. There has been a small number of reports of a similar syndrome following receipt of the Johnson&Johnson /Janssen COVID-19 vaccine (another adenovirus vector vaccine) in the USA. Following a detailed investigation and temporary pause in the use of the vaccine in the USA, the CDC and FDA announced the resumption of the use of the Johnson&Johnson /Janssen vaccine on 23rd April 2021. This vaccine is not currently approved for use in the UK. There is currently no evidence to suggest these rare events have occurred in the UK following administration of either the Pfizer/BioNTech or Moderna COVID-19 vaccines.

Updated Advice issued by UK Joint Committee on Vaccination and Immunisation (JCVI) on Use of AZ Vaccine

The Joint Committee on Vaccination and Immunisation (JCVI) has carefully assessed the overall risk benefit of the use of the AZ vaccine in the UK population. After considering the relative balance of benefits (in terms of deaths, ICU and hospital admissions averted) and risks (based on reported adverse events through the Yellow Card Scheme), on 7 April 2021, JCVI advised that, for adults aged <30 years without underlying health conditions that put them at higher risk of severe COVID-19 disease, there should be a preference for an alternative to the AZ COVID-19 vaccine, if available.

JCVI has continued to review the available data on the current epidemiology, benefit-risk profile by age, modelling predictions on future disease trends and the current forecast on vaccine supply. Given the risk (albeit extremely rare) of these adverse events associated with the AZ vaccine, the current control of COVID-19 in the UK, model predictions of the potential scale and timing of a future wave, and promising forecasts for the availability of vaccines in the UK, on 7th May, the JCVI has issued the following updated advice:

- In addition to those aged under 30, **unvaccinated adults aged 30 - 39 years who are not in a clinical priority group at higher risk of severe COVID-19 disease, should be preferentially offered an alternative to the AZ vaccine**, where possible and only where no substantial delay or barrier in access to vaccination would arise.
- For those aged 18-29 years the precautionary advice for a vaccine preference is stronger, reflecting a gradient in the benefit-risk balance with age.
- For adults aged 40 years and above and those below 40 years with underlying clinical conditions, the overall risk benefit assessment remains in favour of continuing use of the AZ vaccine.

This advice is specific to the current UK context and is based on the prevailing favourable epidemiology of disease, availability of alternatives to the Astra-Zeneca vaccine, and strength of the vaccine programme.

Those who have received their first dose of AZ vaccine without suffering this rare side-effect, should continue to be offered the second dose to complete the course.

Cautions and contraindications for use of AZ Vaccine

Currently there have not been any underlying risk factors that have been identified. There is no evidence to indicate that individuals with a prior history of thrombosis or known risk factors for thrombosis (including those on the oral contraceptive pill) are at increased risk of developing this immunological reaction following vaccination with

the AZ vaccine. Furthermore, for the majority of individuals, the risk of recurrent thrombosis due to COVID-19 infection is far greater than the risk of this syndrome. More than a fifth of hospitalised patients with COVID-19 have evidence of blood clots, and the presence of these almost doubles the risk of death. A revision to the COVID-19 Green book chapter is available with updated information on cautions and contraindications for the AZ vaccine.

There have not been any confirmed cases of this syndrome in pregnant women to date, and prothrombotic states such as pregnancy and contraception are not likely to confer a higher risk. However, because of more extensive experience and use of the Pfizer and Moderna vaccines in pregnant women in the USA, these vaccines are preferred in pregnancy.

Case Reporting

It is very important that all suspected cases are reported to both the MHRA on the COVID-19 Yellow Card scheme and to PHE's clinical reporting scheme at https://cutt.ly/haem_AE. The PHE clinical reporting scheme collects patient identifiable information with details of the clinical presentation, dates of vaccination, vaccine product received and any underlying conditions. In order to minimise burden on reporters, for cases reported on the PHE clinical reporting scheme first, the last page of the survey allows all the inputted answers to be copied, and relevant information can then be directly pasted into the COVID-19 Yellow Card form.

Clinical Investigation and Management

It is important to ensure all health professionals are alert to relevant symptoms which require further clinical review and investigation. It is recommended that an urgent full blood count be considered in any patient presenting more than 4 days and within 28 days of coronavirus vaccination with:

- New onset of severe headache, which is getting worse and does not respond to simple painkillers
- An unusual headache which seems worse when lying down or bending over, or may be accompanied by blurred vision, nausea and vomiting, difficulty with speech, weakness, drowsiness or seizures
- New onset of unexplained pinprick bruising or bleeding
- Shortness of breath, chest pain, leg swelling or persistent abdominal pain

Patients should be urgently referred to hospital and to appropriate specialist services for further assessment, particularly if the symptoms are unexplained and present in combination with thrombocytopaenia. Further guidance for secondary care are available here with specific guidance produced for Emergency Departments and Acute Medical Units and primary care.

The Green Book has been updated and a range of resources for the public and health professionals have been made available. These resources will continue to be updated as new information becomes available, so we recommend linking to the collection to ensure that you are providing the most up-to-date guidance: COVID-19 vaccination and blood clotting - GOV.UK (www.gov.uk)

Implications and recommendations for PHE Regions

PHE Regions are asked to note the updated advice on the use of the AZ vaccine and guidance available for primary and secondary care. PHE Regions are requested to cascade this briefing note to local primary and secondary care services to ensure colleagues are aware of the available guidance and how to report suspected cases.

Implications and recommendations for PHE sites and services

PHE sites and services are asked to note the updated advice on the use of the AZ vaccine and guidance for reporting, investigating and managing suspected cases.

Implications and recommendations for PHE Screening and Immunisation teams

An increase in calls requesting advice are expected. Screening and immunisation teams are requested to note the updated information and guidance. SITs are requested to cascade this briefing note to their local primary care teams.

Implications and recommendations for local authorities

Local Authorities are asked to note the updated advice on the use of the AZ vaccine and guidance for primary and secondary care.

Recommendations for NHS trusts and COVID-19 immunisation services

Services are asked to ensure that anyone being offered an AZ COVID-19 vaccination is given the COVID-19 vaccination and blood clotting guide before vaccination. All people receiving any COVID-19 vaccine should be given the patient vaccination leaflet 'What to expect after vaccination' and know to seek appropriate healthcare assistance if required. These resources have been updated to reflect that latest guidance. All leaflets are available to order as paper copies and in other accessible formats including translations. Primary care services should be aware of these symptoms and refer to secondary care as appropriate following assessment.

References

(1) MHRA: Coronavirus vaccine - weekly summary of Yellow Card reporting (updated 28th 2April 2021) Coronavirus (COVID-19) vaccine adverse reactions - GOV.UK (www.gov.uk)

(2) PHE: Impact of COVID-19 vaccines on mortality in England (December 2020 to March 2021) PHE monitoring of the effectiveness of COVID-19 vaccination - GOV.UK (www.gov.uk)

(3) Public Health England vaccine effectiveness report (March 2021) PHE monitoring of the effectiveness of COVID-19 vaccination - GOV.UK (www.gov.uk)

Sources of information

Coronavirus Yellow Card reporting site Official MHRA side effect and adverse incident reporting site for coronavirus treatments and vaccines | Coronavirus (COVID-19)

Public Health England: Thrombotic events with thrombocytopenia following immunisation to COVID-19 https://cutt.ly/haem_AE

Guidance produced from the Expert Haematology Panel (EHP) focussed on syndrome of Thrombosis and Thrombocytopenia occurring after coronavirus Vaccination https://b-s-h.org.uk/about-us/news/guidance-produced-by-the-expert-haematology-panel-ehp-focussed-on-vaccine-induced-thrombosis-and-thrombocytopenia-vitt/

Vaccine Pathway Concerns – RCEM/SAM/RCP guidance Vaccine pathway concerns - RCEM/SAM/RCP guidance

MHRA issues new advice, concluding a possible link between COVID-19 Vaccine AstraZeneca and extremely rare, unlikely to occur blood clots https://www.gov.uk/government/news/mhra-issues-new-advice-concluding-a-possible-link-between-covid-19-vaccine-astrazeneca-and-extremely-rare-unlikely-to-occur-blood-clots

Use of the AstraZeneca COVID-19 vaccine: JCVI statement https://www.gov.uk/government/publications/use-of-the-astrazeneca-covid-19-vaccine-jcvi-statement

JCVI final statement on phase 2 of the COVID-19 vaccination programme: 13 April 2021 JCVI final statement on phase 2 of the COVID-19 vaccination programme: 13 April 2021 - GOV.UK (www.gov.uk)

Use of the AstraZeneca COVID-19 (AZD1222) vaccine: updated JCVI statement, 7 May 2021 https://www.gov.uk/government/publications/use-of-the-astrazeneca-covid-19-vaccine-jcvi-statement-7-may-2021/use-of-the-astrazeneca-covid-19-azd1222-vaccine-updated-jcvi-statement-7-may-2021

COVID-19 vaccination and blood clotting resources https://www.gov.uk/government/collections/covid-19-vaccination-and-blood-clotting

Blood Clotting following COVID-19 Vaccination - Information for Health Professionals https://www.gov.uk/government/collections/covid-19-vaccination-and-blood-clotting

COVID-19 vaccination and blood clotting guide version 2 https://www.gov.uk/government/publications/covid-19-vaccination-and-blood-clotting
This should be given to anyone offered the AstraZeneca vaccination. Copies will be available to order using product code: COV2020700V2 from Health Publications website: https://www.healthpublications.gov.uk/Home.html
Large orders can be placed by phone: 0300 123 1002

COVID-19: the green book, chapter 14a - GOV.UK (www.gov.uk)

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RCGP Primary Care Management of Suspected Thromboembolism with Thrombocytopenia after COVID-19 Vaccination Headaches after AZ_April 2021 (rcgp.org.uk)