PHS Health Protection Alert

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| Title | Description |
| Event | National incident in response to reports of thrombosis with thrombocytopenia following vaccination with the COVID-19 AstraZeneca vaccine (Update) |
| Alert reference number | 2021/09 |
| Recipients of this alert | Directors of Public Health, Health Protection Teams, Cell Leads, Scottish Government, Chief Medical Officers, NHS24, Immunisation Co-ordinators, FVCV PMO, FVCV Clinical Governance Group |
| Alert status | 4. for action - monitoring, wider dissemination and specific measures to be taken by recipient |
| Action required of initial recipients | * Cascade to others for action, as indicated
 |
| Date of issue | 21/04/2021 |
| Source of event information | <https://www.gov.uk/government/publications/priority-groups-for-phase-2-of-the-coronavirus-covid-19-vaccination-programme-advice-from-the-jcvi/jcvi-final-statement-on-phase-2-of-the-covid-19-vaccination-programme-13-april-2021><https://coronavirus-yellowcard.mhra.gov.uk/> <https://www.gov.uk/government/publications/covid-19-the-green-book-chapter-14a>  |
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| Authorised by | Dr Jim McMenamin, Incident Director for Covid-19 |
| HPZone context | AstraZeneca Vaccine Safety |

# Situation

## The overall benefits of vaccination continue to outweigh any risks but the MHRA and JCVI have issued updated advice for particular groups including adults under age 30 years and pregnant women. A revised Green Book chapter is available and clinical advice on case investigation and management has been issued.

# Background

This an update to alerts 2021/06 (7th April 2021) and 2021/07 (10th April) relating to the UK national incident response to reports of thrombosis with thrombocytopenia following the AstraZeneca (AZ) COVID-19 vaccine. Since its deployment on the 4th January 2021, an estimated 21.6 million doses of the AZ vaccine have been administered across the UK (1). The COVID-19 programme has been estimated to have prevented more than 10,000 deaths in adults aged 70 years and older till the end of March (2) with a vaccine effectiveness of a single dose against hospitalisation estimated at 80% both the Pfizer/BioNTech and the AZ vaccines (3).

As of 5th April, there have been 100 reports of thromboembolic events occurring with thrombocytopenia across the UK following AZ vaccination, giving an overall case incidence of 4.9 per million first doses (1). This includes 50 reports 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. The remaining 50 reports of other thromboembolic events includes both venous and arterial thrombotic events. 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 cerebral venous sinus thrombosis and portal vein thrombosis, as well as the more usual presentations of deep vein thrombosis and pulmonary embolism. Arterial events are increasingly being recognised too. Typical laboratory features include a low platelet count, very raised D-Dimer levels which are above the level expected for venous thromboembolism (VTE), and inappropriately low fibrinogen. 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 case fatality rates estimated to be 22% (notably lower than those reported from some other countries).

Although these extremely rare events have been associated with the AZ vaccine, further investigations are underway to understand the biological mechanisms and whether the association is related to the vaccine platform (the way in which the vaccine delivers antigen) or some other immunological mechanism. Of note, there has been a small number of reports of a similar syndrome following receipt of the J&J/Janssen COVID-19 vaccine (another adenovirus vector vaccine) in the USA. As a precaution, the US FDA and CDC announced a pause in the use of the J&J/Janssen vaccine. Similar advice has been issued in some European countries whilst investigations are ongoing and the European Medicines Agency has issued a [statement](https://www.ema.europa.eu/en/news/covid-19-vaccine-janssen-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood) . This vaccine is not currently approved for use in the UK. There is currently no evidence to suggest these rare events occur following administration of either the Pfizer/BioNTech or Moderna vaccines which are available in the UK.

Assessment

The current MHRA advice remains that the overall benefits of the COVID-19 vaccine programme outweighs the extremely rare adverse events reported to date following the AZ vaccine. This is based on a review of cases reported to the Yellow Card Scheme and the evidence of effectiveness of the COVID vaccines used in the UK to prevent serious complications and deaths from COVID-19 infection,

The Joint Committee on Vaccination and Immunisation (JCVI) has also assessed the overall risk benefit of the use of the AZ vaccine in the population. This is based on data presented by the MHRA on reported adverse events through the Yellow Card Scheme and benefits (in terms of deaths, ICU and hospital admissions averted) estimated by Public Health England. This took into account the trend of increasing incidence of this condition with decreasing age amongst adults, and the age-related risks of serious disease associated with COVID-19 which increase steeply with age. Whilst for adults aged 30 years and above and those below 30 years with underlying clinical conditions, the overall risk benefit assessment was in favour of continuing use of the AZ vaccine, the [JCVI has concluded that in phase 2](https://www.gov.uk/government/publications/priority-groups-for-phase-2-of-the-coronavirus-covid-19-vaccination-programme-advice-from-the-jcvi/jcvi-final-statement-on-phase-2-of-the-covid-19-vaccination-programme-13-april-2021) of the vaccination programme, it is preferable to offer adults under 30 years of age without underlying health conditions putting them at a higher risk of severe COVID-19 disease, an alternative to the AZ vaccine if available. Individuals can make an informed choice to receive the AZ vaccine to receive earlier protection.

Cautions and contraindications for use of AZ Vaccine

Currently there have not been any underlying risk factors that have been identified. Based on the cases reviewed by the Expert Haematology Panel to date, they advise that 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 recent [preprint of a study](https://osf.io/a9jdq/) based on analysis of US data showed that CVST was a frequent complication of COVID-19 infection, at a rate higher than that seen after vaccination. A revision to the [COVID-19 Green book chapter](https://www.gov.uk/government/publications/covid-19-the-green-book-chapter-14a) 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 safety data for Pfizer and Moderna vaccines from 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](https://coronavirus-yellowcard.mhra.gov.uk/) 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

A detailed case review is ongoing jointly by MHRA, PHE and the UK Expert Haematology Panel. It is important to ensure all health professionals are alert to relevant symptoms which require further clinical review and investigation. As the recommended management of this presenting condition differs from the usual guidance, urgent advice has been cascaded to primary care to ensure GPs are on the alert for this syndrome. Advice from RCGP is also [available](https://elearning.rcgp.org.uk/mod/page/view.php?id=11513). 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

If you have any clinical concerns, 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 thrombocytopenia. Further guidance for secondary care are available [here](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/) with specific guidance produced for [Emergency Departments and Acute Medical Units](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/).

Mild flu-like symptoms, including headache, chills and fever remain one of the most common side effects of any COVID-19 vaccine. These generally appear within a few hours and resolve within a day or two.

The [Green Book](https://www.gov.uk/government/publications/covid-19-the-green-book-chapter-14a) has been updated and a range of resources for the public and health professionals have been made available at [NHS Inform](https://www.nhsinform.scot/covid-19-vaccine) and [NHS Education for Scotland](https://www.nes.scot.nhs.uk/nes-current/covid-19-vaccination-programme/). These resources will continue to be updated as new information becomes available.

# Recommendations

NHS Boards are asked to note the current information and guidance for primary and secondary care. NHS Boards are requested to cascade this alert to local primary and secondary care services to ensure colleagues are aware of the available guidance and how to report suspected cases.

An increase in calls requesting advice are expected. Immunisation teams are requested to note the current information and guidance and to cascade this alert note which includes additional specific guidance developed for primary care with their local primary care teams.

COVID-19 immunisation services are asked to ensure that people receiving a COVID-19 vaccine are given the NEW patient vaccination leaflet ‘COVID-19 AstraZeneca vaccine and rare blood clots'’. Printed copies have been sent to vaccination sites and the information is online at NHS inform. The main vaccination leaflets have also been updated including the usual ‘COVID-19 adult leaflet' provided with invitation letter. You should also ensure that patients are given ‘What to expect after vaccination’ after vaccination and know to seek appropriate healthcare assistance if required. These resources have been updated to reflect that latest guidance. Primary care services should be aware of these symptoms and refer to secondary care as appropriate following assessment. Updated versions of the above leaflets will be available [here](https://www.nhsinform.scot/covid19vaccineleaflets).

References

(1) MHRA: Coronavirus vaccine - weekly summary of Yellow Card reporting (updated 15th April 2021) Coronavirus (COVID-19) vaccine adverse reactions - GOV.UK (www.gov.uk) <https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions>

(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) <https://www.gov.uk/government/publications/phe-monitoring-of-the-effectiveness-of-covid-19-vaccination>

(3) Public Health England vaccine effectiveness report (March 2021) PHE monitoring of the effectiveness of COVID-19 vaccination - GOV.UK (www.gov.uk) <https://www.gov.uk/government/publications/phe-monitoring-of-the-effectiveness-of-covid-19-vaccination>; [COVID-19 vaccine linked to a reduction in transmission - News - Public Health Scotland](https://www.publichealthscotland.scot/news/2021/march/covid-19-vaccine-linked-to-a-reduction-in-transmission/); [Vaccine linked to reduction in risk of COVID-19 admissions to hospitals - News - Public Health Scotland](https://www.publichealthscotland.scot/news/2021/february/vaccine-linked-to-reduction-in-risk-of-covid-19-admissions-to-hospitals/)

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)](https://coronavirus-yellowcard.mhra.gov.uk/)

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](https://www.rcem.ac.uk/docs/Policy/ED-AM%20%20Vaccine%20pathway%20concerns%20-%20RCP%20-%20SAM%20-%20RCEM.pdf)

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 - <https://www.gov.uk/government/publications/priority-groups-for-phase-2-of-the-coronavirus-covid-19-vaccination-programme-advice-from-the-jcvi/jcvi-final-statement-on-phase-2-of-the-covid-19-vaccination-programme-13-april-2021>

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

<https://www.nhsinform.scot/covid-19-vaccine>

<https://www.nes.scot.nhs.uk/nes-current/covid-19-vaccination-programme/> (including 21 April 2021 webinar recording)

COVID-19: the green book, chapter 14a - <https://www.gov.uk/government/publications/covid-19-the-green-book-chapter-14a>