Public Health England

NHS

Blood Clotting following COVID-19 Vaccination

Information for Health Professionals

As with all COVID-19 programme resources, this publication is subject to extensive and regular revisions and we recommend linking to the latest version to ensure that you are giving the most up-to-date clinical advice and guidance.

A range of resources have been developed and updated to support this decision making and are available at **www.gov.uk/government/collections/covid-19-vaccination-and-blood-clotting**.

1. What is the condition that has been reported following COVID-19 vaccination?

In recent weeks, there have been a small number of reports from the UK and internationally of an extremely rare condition characterised by thromboembolic events (blood clots) accompanied by thrombocytopenia (low platelets) following the first dose of the AstraZeneca (AZ) COVID-19 vaccination.

The most notable presentation is cerebral venous sinus thromboses (CVST) where blood clots develop in the cerebral veins occurring together with low platelet counts. These cases are particularly unusual because despite low platelets, there is progressive thrombosis (formation of blood clots which block blood vessels). Whilst the cases reported to date have primarily been venous clots, arterial clots have also been reported. All cases reported in the UK to date have occurred after the first dose of AZ vaccine.

Typical laboratory features include a low platelet count, very raised D Dimer levels – above the level expected for venous thromboembolism (VTE) and inappropriately low fibrinogen. Antibodies to platelet factor 4 (PF4) have been identified and so this has similarities to heparin-induced thrombocytopenia (HIT), but is occurring without the patient receiving any heparin treatment.

Further information on the investigation and treatment of suspected cases has been published by the Expert Haematology Panel of the British Society of Haematology and is available at weblink 1.

2. What are the risk factors for developing this condition?

This condition is known to occur naturally although the underlying risk factors have not yet been fully established. A detailed review of suspected cases of this condition following COVID vaccination is ongoing by the Medicines Healthcare products Regulatory Agency (MHRA), supported by PHE and other professional groups.

This will help us to understand the risk factors for developing this condition. The current data suggests that the overall incidence is around 4 per million first doses of the AZ vaccine administered. Although cases have been reported in all ages and genders, there appears to be a trend for increasing incidence with decreasing age amongst adults, with the highest incidence reported in the younger adult age groups.

3. Is this condition only associated with the AZ vaccine?

All suspected cases following vaccination with any of the COVID-19 vaccines being used in the UK are undergoing a detailed review by the MHRA. Up to and including 31st March, the MHRA received 79 reports of thrombosis events with low platelets of which 44 were cerebral venous sinus thrombosis (CVST), out of a total of 20.2 million doses of COVID-19 AZ vaccine given by that date. Two cases of blood clots (thromboembolism) with thrombocytopenia were reported for the Pfizer/BioNTech vaccine up to and including 31st March, but a detailed medical review by the MHRA concluded that these were very unlikely to be related to the vaccine.

There is currently no evidence to suggest these rare events occur with the Pfizer/BioNTech vaccine. 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.

4. How many people have developed the condition?

This condition is known to occur naturally and is thought to be extremely rare. The background rate of cerebral venous sinus thromboses (CVSTs) is estimated to be around 5 to 16 per million annually, although there is currently limited data on the background rate of CVSTs occurring without thrombocytopenia. It is currently estimated that the overall incidence following the AZ vaccine is around 4 per million first doses administered. It is also important to note that thromboses (blood clots) have been reported with natural COVID-19 infection and more than a fifth of hospitalised patients with COVID-19 have evidence of blood clots.

Internationally, there have been a very small number of reports of thromboembolic events accompanied by thrombocytopenia following AZ vaccine.

5. How many of those affected die?

A detailed review of all suspected cases is ongoing and based on the reports received by the MHRA as of 31st March, there were 19 fatal cases from the 79 events reviewed. This compares with the clear demonstrable benefits from the COVID vaccination programme.

Since the 4th January more than 20.2 million doses of the AZ vaccine have been administered across the UK. It has been estimated that the vaccine programme has prevented 6,100 deaths in adults aged 70 years and older up to the end of February with a vaccine effectiveness of a single dose against hospitalisation estimated at 80% for both the Pfizer/BioNTech and the AZ vaccines.

6. Why isn't the UK suspending use of the AZ vaccine?

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 current MHRA advice remains that the overall benefits of the vaccine programme outweighs the extremely rare adverse events reported to date following the AZ vaccine.

The Joint Committee on Vaccination and Immunisation (JCVI) has 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. Given the very small numbers of events reported overall, there is currently a high level of uncertainty in the estimates of the incidence of this condition by age group.

There appears to be a trend of increasing incidence of this condition with decreasing age amongst adults, with the highest incidence reported in the younger adult age groups. In contrast, the risks of serious disease associated with COVID-19 increases steeply with age, with the younger adults at the lowest risk of serious disease. Amongst those healthy adults under 50 years, there continues to be an age-related risk of severe complications from COVID-19. For example, the risk of dying in an individual aged 40-49 years is 3 times higher than someone aged 30-39 years and 12 times higher than someone aged 20-29 years.

Therefore, weighing the balance of benefits and risks, currently the JCVI has concluded that for adults under 30 years of age who are not in a clinical risk group, it is preferable to offer an alternative to the AZ vaccine if available (see weblink 2).

The AZ vaccine should continue to be offered to those in Phase 1 (which includes older adults, those with underlying conditions, health and social care workers over 30 years old) who have not yet been offered the vaccine. Those who have received their first dose of AZ vaccine should continue to be offered the second dose to complete the course. Individuals aged 18 to 29 years who have received their first dose of AZ vaccine as part of the Phase 1 programme, without suffering any serious side effects, should complete their course with the same vaccine. This includes those who are health and social care workers, unpaid carers and family members of those who are immunosuppressed. Healthy adults aged 30-50 years who will be offered vaccine as part of the second phase of the programme are recommended to receive any of the available COVID-19 vaccines.

Those who have received their first dose of AZ vaccine should continue to be offered the second dose to complete the course.

As the deployment of the second phase of the programme gets underway, the JCVI are committed to undertaking a detailed and ongoing review as each age group becomes eligible for vaccination based on the current epidemiology, the latest information on reported cases to the MHRA and vaccine availability.

7. Can COVID-19 infection cause the same problem?

Thrombotic events have also occurred in individuals with natural COVID-19 infection and more than a fifth of hospitalised patients with COVID-19 have evidence of blood clots.

However, this particular combination of thrombotic events and thrombocytopenia is extremely rare and not known to be a common feature of COVID-19 infection.

8. Has this condition been reported after both the 1st and 2nd dose of COVID-19 vaccine?

To date, the small number of these extremely rare events that have been reported to the MHRA have occurred after the first dose of the AZ vaccine. Whilst currently there is no evidence to suggest whether these rare events are dose specific it is important to note that most vaccines in the UK COVID programme have been administered as first doses. The JCVI advises that those who have received their first dose of AZ vaccine should continue to be offered the second dose.

9. Is it affecting both men and women?

Suspected cases have been reported in patients of all ages in men and women. Whilst reports from some countries have suggested a substantially higher number of cases amongst females, based on the events reported to the MHRA in the UK, such a distinctive gender difference has not been observed.

It is worth noting that more females have been vaccinated which may partly explain the slight excess of cases reported amongst females.

10. Is it affecting any particular community?

Suspected cases have been reported in patients of all ages and genders and currently, no specific predisposing factors have been identified.

11. What are the signs and symptoms?

While the detailed case review is ongoing, it is important to ensure all health professionals are alert to relevant symptoms which require further clinical review and investigation. Advise patients to seek urgent medical advice if they experience any of the following symptoms more than 4 days and within 28 days of coronavirus vaccination:

- 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 unexplained pinprick bruising or bleeding
- shortness of breath, chest pain, leg swelling or persistent abdominal pain

If you have clinical concern, 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 at weblink 1.

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.

12. What should I do if I suspect a case?

If you have 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 thrombocytopaenia. Further guidance for secondary care are available at weblink 1.

In the UK, the MHRA are reviewing all reported cases to the COVID-19 Yellow Card scheme. In order to support the case reporting, clinical review and investigation, PHE has established an electronic clinical reporting scheme collecting patient identifiable information on all suspected cases. All health professionals are also encouraged to report any suspected case at https://cutt.ly/haem_AE with details of the clinical presentation, dates of vaccination, vaccine product received and any underlying conditions.

13. How should I report suspected cases?

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.

14. Are there any contraindications or cautions to receiving the AZ vaccine?

The contra-indications to vaccination with the AZ COVID-19 vaccine include individuals who have a history of other extremely rare immune-mediated syndromes that are characterised by thrombosis in combination with thrombocytopaenia – this includes a previous episode of Heparin-Induced Thrombocytopaenia or the same specific clinical picture in association with anti-phospholipid syndrome. These individuals may be offered vaccination with an alternative COVID-19 vaccine. A history of thromboses on its own is not a contraindication to the vaccine. The Green Book has further information on contraindications and cautions to receiving the AZ vaccine.

Individuals over 30 years of age with past clotting episodes and those diagnosed with thrombophilia, whether or not they are on long term anti-coagulation, remain at risk of COVID-19 disease and should be vaccinated with any of the available vaccines (provided they are not otherwise contra-indicated). The same consideration applies to those who experience common clotting episodes, without concomitant thrombocytopaenia, after the first dose of Astra-Zeneca vaccine.

The Expert Haematology Panel advise that there is no evidence that individuals with a prior history of thrombosis or known risk factors for thrombosis are more at risk of developing the immune complication reported after the AstraZeneca 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.

15. Should we still give people their second dose?

Yes, because of the high risk of complications and death from COVID, the MHRA, the World Health Organisation and the European Medicines Agency have concluded that the balance is very much in favour of vaccination. All of the events reported to date have occurred after the first dose of the AZ vaccine. There are currently no known risk factors for this extremely rare condition, which appears to be an idiosyncratic reaction on first exposure to the AZ COVID-19 vaccine. The JCVI advises that those who have received their first dose of AZ vaccine should continue to be offered the second dose.

16. Can my patient receive the AZ vaccine if they have previously had a blood clot?

Importantly, a history of thromboses on its own is not a contraindication to the vaccine and individuals should be reassured that they can still receive the AZ vaccine when offered.

The contra-indications to vaccination with the AZ COVID-19 vaccine include individuals who have a history of other extremely rare immune-mediated syndromes that are characterised by thrombosis in combination with thrombocytopaenia – this includes a previous episode of Heparin-Induced Thrombocytopaenia or the same specific clinical picture in association with anti-phospholipid syndrome. These individuals may be offered vaccination with an alternative COVID-19 vaccine.

Individuals over 30 years of age with past clotting episodes and those diagnosed with thrombophilia, whether or not they are on long term anti-coagulation, remain at risk of COVID-19 disease and should be vaccinated with any of the available vaccines (provided they are not otherwise contra-indicated). The same consideration applies to those who experience common clotting episodes, without concomitant thrombocytopaenia, after the first dose of Astra-Zeneca vaccine.

The Expert Haematology Panel advise that there is no evidence that individuals with a prior history of thrombosis or known risk factors for thrombosis are more at risk of developing the immune complication reported after the AstraZeneca 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.

If a patient has a history of, for example, a deep venous thrombosis (DVT) or pulmonary embolus (PE) without concurrent thrombocytopenia, then they can receive the AZ vaccine. Likewise, if they have had an arterial thrombosis e.g. myocardial infarction without thrombocytopenia then they can receive the AZ vaccine.

Many patients who have had a history of blood clots may be concerned as to whether they also had low platelets at the same time. This is likely to have been communicated at the time of diagnosis of the blood clot and be recorded in the patient's medical records. In the absence of this being recorded in the patient's medical records, such individuals can be offered the AZ vaccine.

17. Can my patient receive the AZ vaccine if they have been or are currently thrombocytopenic?

Thrombocytopaenia on its own is not a contraindication to receiving the AZ vaccine.

The contra-indications to vaccination with the AZ COVID-19 vaccine include individuals who have a history of other extremely rare immune-mediated syndromes that are characterised by thrombosis in combination with thrombocytopaenia – this includes a previous episode of Heparin-Induced Thrombocytopaenia or the same specific clinical picture in association with anti-phospholipid syndrome. These individuals may be offered vaccination with an alternative COVID-19 vaccine.

Individuals with bleeding disorders can still be vaccinated and further information is available in the Green Book.

18. What if someone has had a cerebral or major blot clot with low levels of platelets following the first dose of AZ vaccine?

Anyone who experienced cerebral or other major blood clots occurring with low levels of platelets after their first vaccine dose of COVID-19 Vaccine AZ should not have their second dose of AZ vaccine.

19. Can my patient still have a second dose AZ vaccine if they had a blood clot after the first dose?

Importantly, a history of thromboses on its own (without thrombocytopaenia) following the first dose of AZ vaccine is not a contraindication to receiving their second dose and individuals should be reassured that they can still receive the AZ vaccine when offered.

The contra-indications to vaccination with the AZ COVID-19 vaccine include individuals who have a history of other extremely rare immune-mediated syndromes that are characterised by thrombosis in combination with thrombocytopaenia – this includes a previous episode of Heparin-Induced Thrombocytopaenia or the same specific clinical picture in association with anti-phospholipid syndrome. These individuals may be offered vaccination with an alternative COVID-19 vaccine.

The Expert Haematology Panel advise that there is no evidence that individuals with a prior history of thrombosis or known risk factors for thrombosis are more at risk of developing the immune complication reported after the AstraZeneca 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. Individuals who experience a clotting episode WITH concomitant thrombocytopenia following the first dose of AstraZeneca vaccine should be properly assessed; if they are considered to have the reported condition, further vaccination should be deferred until their clotting has completely stabilised and should then be boosted with an alternative product.

In the UK about 1 in a 1000 people are affected by venous thrombosis each year. This compares with reports up to the 31st March to the MHRA of 79 thrombosis events with low platelets out of a total of 20.2 million doses of COVID-19 AZ vaccine given by that date. Therefore, by chance a lot of people will have blood clots after vaccination which are not due to this syndrome.

20. What if somebody under 30 years has had AZ for their first dose – should they have the second?

The AZ vaccine should continue to be offered to those in Phase 1 who have not yet been offered the vaccine. This includes older adults, those with underlying conditions, health and social care workers over 30 years old. All of the events reported to date have occurred after the first dose of the AZ vaccine.

There are currently no known risk factors for this extremely rare condition, which appears to be an idiosyncratic reaction on first exposure to the AZ COVID-19 vaccine. Those who have received their first dose of AZ vaccine should continue to be offered the second dose.

Individuals aged 18 to 29 years who have received their first dose of AZ vaccine as part of the Phase 1 programme, without suffering any serious side effects, should complete their course with the same vaccine. This includes those who are health and social care workers, unpaid carers and also family members of those who are immunosuppressed.

There is currently no evidence on the interchangeability of the COVID-19 vaccines although studies are underway. Therefore, every effort should be made to determine which vaccine the individual received and to complete with the same vaccine. Please see the Green Book for further advice on vaccination.

21. Will taking aspirin before vaccination with the AZ vaccine reduce the clotting risk for my patients'?

It is NOT recommended to take aspirin before vaccination with AZ, unless this is already part of your patient's regular medications.

Investigations are underway to understand the biological mechanisms behind this extremely rare condition of thromboembolic events with thrombocytopenia and whether the association is related to the vaccine platform (the way in which the vaccine delivers antigen) or some other immunological mechanism. Whilst aspirin may be used to reduce clotting risk in other conditions, it is not currently thought to have the same effect in this condition and may in fact worsen the outcome by increasing the risk of bleeding. Therefore no one should self-medicate with aspirin to cover the period around and after the vaccination.

22. How can I communicate the potential benefits and risks of the AZ vaccine to my patients?

The Winton Centre for Risk and Evidence Communication at the University of Cambridge has developed some materials for communicating potential benefits and risks of the AZ vaccine. This considers the benefits (in terms of preventing Intensive Care Unit (ICU) admissions) and AZ vaccine risk at different exposure levels of COVID-19, (from low, medium and high incidence of COVID-19), which is broken down by age bands.

Where there is a low exposure risk of COVID-19, (incidence of 2 in 10,000 per day) which reflects the situation in the UK in March 2021, the potential harm of specific blood clots due to the AZ vaccine and potential benefit of the vaccine by age group has been estimated as follows:

- For people aged 30 – 39, potential harm was 0.8 per 100,000 people and potential benefit was 2.7 per 100,000 people
- For people aged 50-59, potential harm was 0.4 per 100,000 people and potential benefit was 10.5 per 100,000 people

Where the exposure risk of COVID-19 is medium, (incidence of 6 in 10,000 per day) reflecting the situation in the UK during February 2021, the potential benefits from vaccination are even greater:

- For people aged 30-39, potential harm was 0.8 per 100,000 people and potential benefit was 8 per 100,000 people
- For people aged 50-59, potential harm was 0.4 per 100,000 people and potential benefit was 31 per 100,000 people

Someone who is vaccinated will continue to accrue benefits from vaccination over their lifetime from being protected to COVID-19, whilst the risk from vaccination occurs only in the few weeks after vaccination. The model only considers the benefits from avoiding ICU admission but there are other benefits to vaccination, such as avoiding hospitalisation or long COVID, and of not spreading the virus to other people. Further information and age band specific potential benefits and risks are available at https://wintoncentre.maths.cam.ac.uk/news/communicating-potential-benefits-and-harms-astra-zeneca-covid-19-vaccine/

23. What if my patient refuses the AZ vaccine?

To make an informed decision it is important that all individuals are provided with the relevant information, including the benefits and risks, and that they have the opportunity to discuss this with their healthcare provider if they wish. If the patient is under 30 an alternative vaccine will become available but they may have to wait for other supplies.

24. What if my patient under 30 years old wants to have the AZ vaccine?

Patients under 30 who decide to go ahead after they have considered all the risks and benefits can be vaccinated with the AZ vaccine. You should document that you have had a full conversation with the patient and that you have provided them with sufficient information for them to give informed consent to vaccination.

Blood Clotting following COVID-19 Vaccination

Information for Health Professionals

Sources

Guidance produced from the Expert Haematology Panel (EHP) focussed on syndrome of Thrombosis and Thrombocytopenia occurring after coronavirus Vaccination Guidance produced from the Expert Haematology Panel (EHP) focussed on syndrome of Thrombosis and Thrombocytopenia occurring after coronavirus Vaccination | British Society for Haematology (b-s-h.org.uk)

COVID-19: the green book, chapter 14a COVID-19 Greenbook chapter 14a (publishing.service.gov.uk)

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

MHRA issues new advice, concluding a possible link between COVID-19 Vaccine AstraZeneca and extremely rare, unlikely to occur blood clots 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

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 – reporting Thrombotic events with thrombocytopenia following immunisation to COVID-19 https://cutt.ly/haem_AE

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

Expert Haematology Panel: https://b-s-h.org.uk/media/19537/letter-to-mhra-from-expert-haematology-group-endorsed-by-thrombosis-uk-1300-8th-april-2021.pdf

Weblink 1: https://b-s-h.org.uk/about-us/news/guidance-produced-from-the-expert-haematology-panel-ehp-focussed-on-syndrome-of-thrombosis-and-thrombocytopenia-occurring-after-coronavirus-vaccination/

Weblink 2: https://www.gov.uk/government/publications/use-of-the-astrazeneca-covid-19-vaccine-jcvi-statement

Vaccination, helping to protect those most vulnerable.