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COVID-19 vaccine

HSC Health and Social Care

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.

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

Since March 2021 there have been reports from the UK and internationally of an extremely rare condition characterised by thromboembolic events (blood clots) accompanied by thrombocytopaenia (low platelets) following the first dose of the AstraZeneca (AZ) COVID-19 vaccination. This includes 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).

The cases of venous thromboses that have been reported include CVST and portal vein thrombosis, as well as the more usual presentations of deep vein thrombosis and pulmonary embolism. Whilst the cases reported to date have primarily been venous clots, arterial clots have also been reported.

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 thrombocytopaenia (HIT), but it is occurring without the patient receiving any heparin treatment.

Up to 11 August 2021, 412 suspected cases have been reported across the UK through the regulatory agency (MHRA) Yellow Card scheme following AZ vaccination and 43 suspected cases were after the second dose of AZ vaccine. Whilst investigation remains ongoing for some cases, it is important to note that the overwhelming majority of cases reported after the second dose have not been confirmed and remain dramatically lower than after the first dose; there is therefore no evidence of an association of this syndrome with the second dose of AZ vaccine. The JCVI advises that those who have received their first dose of the AZ vaccine should continue to be offered the second vaccine unless they have developed this specific syndrome of thrombosis and thrombocytopaenia following the first dose or if the vaccine is otherwise contraindicated. For the latest information, please see the weekly summary from the MHRA.

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 here.

A recent study provides further information on the clinical features and prognostic criteria of this syndrome.

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 MHRA, supported by PHE and other professional groups. This will help us to understand the risk factors for developing this condition. The data reported in the MHRA weekly report up to 4 August 2021 estimates an overall incidence of around 14.9 per million after first or unknown doses of the AZ vaccine administered in the UK. There is no indication of an increased risk of these events after the second dose. These data are regularly updated based on the reports received through the Yellow Card reporting scheme. For the latest information please see the

weekly summary from the MHRA. 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 4 August 2021, the MHRA received 412 reports of thrombosis events with low platelets of which 147 were cerebral venous sinus thrombosis (CVST) following vaccination with the AZ vaccine. This is out of a total of 24.8 million first doses and 23.9 million second doses of AZ vaccine given by that date in the UK. For the latest information please see the weekly summary from the MHRA.

There has also been a small number of reports of a similar syndrome following receipt of the Johnson & Johnson/Janssen COVID-19 vaccine (also an adenovirus vector vaccine, although using a different vector) 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 vaccine for all age groups on 23 April 2021. There is currently no evidence to suggest these rare events occur following administration of either Pfizer/BioNTech or Moderna vaccines which are available in the UK.

Up to 11 August 2021, the MHRA received 15 reports of thrombosis events with low platelets following vaccination with the Pfizer/BioNTech vaccine. This is out of a total of 20.46 million first doses and 13.8 million second doses of the Pfizer/BioNTech vaccine. Reassuringly, as these numbers are so small, there is no signal of this syndrome with the Pfizer/BioNTech vaccine. There were 2 reports of this syndrome following vaccination with the Moderna vaccine.

Although these extremely rare events have been associated with the AZ vaccine and Johnson & Johnson/Janssen vaccines, 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 with thrombocytopaenia.

Based on reports to 11 August 2021, the overall incidence following the AZ vaccine is around 14.9 per million first or unknown doses administered and 1.8 per million second doses administered. For the latest information please see the weekly summary from the MHRA.

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. A study based on analysis of US data showed that CVST was a complication of COVID-19 infection, with a higher incidence (42.8 per million) compared to a matched cohort of patients with influenza (RR=2.67, 95% CI 1.04-6.81, P<0.031) and people who had received an mRNA vaccine ((RR=6.33, 95% CI 1.87-21.40, P=0.00014).

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 11 August, there were 73 fatal cases from the 411 events reviewed with an estimated overall case fatality rate of 18%. This compares with the clear demonstrable benefits from the COVID vaccination programme. For the latest information please see the weekly summary from the MHRA. Since 4 January to 4 August 2021 24.8 million first doses and 23.9 million second doses of the AZ vaccine have been administered across the UK. It has been estimated that the vaccine programme has prevented between 81,300 and 87,800 deaths up to 6 August with a vaccine effectiveness of a single dose against hospitalisation estimated at 80% for both the Pfizer/BioNTech and the AZ vaccines.

6. What is the UK's current advice on the 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 use of the AZ vaccine in the UK vaccine programme outweighs the extremely rare adverse events reported to date.

Blood Clotting following COVID-19 Vaccination

Information for Health Professionals

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 and continues to keep this under active review. After considering the relative balance of benefits (in terms of deaths, ICU and hospital admissions averted estimated by Public Health England) and risks (based on data presented by the MHRA 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 vaccine, if available.

The MHRA has continued to review cases of these extremely rare adverse events, including those reported retrospectively, and data on the frequency of these events by age are now more precise. The available data continues to suggest 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 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.

JCVI have 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, JCVI has issued updated advice on 7 May 2021.

- 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 within this age group who are of older age, male, obese (BMI >30), from certain ethnic minority backgrounds or experiencing socio-economic deprivation, the risks of acquiring and/ or suffering complications of COVID-19 are higher. Every effort should be made to remove barriers to accessing vaccination in those individuals. These individuals can choose to have the AZ vaccine if they have been provided with information on the risks and benefits of the vaccine.
- 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.

This new advice is specific to the current UK context and is based on all of the following remaining favourable: the current low incidence of disease, the availability of alternatives to the AZ vaccine, and the strength of the whole vaccine programme in terms of maintaining speed and uptake. Should there be a deterioration in any of the above factors, JCVI advises that vaccination of adults aged 30-39 years with any of the UK authorised vaccines is always better than no vaccination, except where there are specific contraindications.

Healthy adults aged 40-50 years who are offered vaccine are recommended to receive any of the available COVID-19 vaccines. 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 (see the Green Book for further information).

The AZ vaccine should also continue to be offered to those in the priority groups (which includes older adults, those with underlying conditions, health and social care workers over 40 years old) who have not yet been offered the vaccine. 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. This includes individuals aged 18 to 39 years who have received their first dose of AZ vaccine in the initial priority groups, which includes those who are health and social care workers, unpaid carers and family members of those who are immunosuppressed.

Due to its storage and transport requirements, the AZ vaccine is much more easily delivered in some settings, and in these settings may be the only vaccine it is practical to offer. In such circumstances JCVI advises that the benefits of receiving the AZ vaccine outweigh the risks, and individuals in this event should be offered the AZ vaccine.

JCVI considers that there continues to be no safety concerns for this extremely rare adverse event following receipt of a second dose of AZ vaccine. All those who have received a first dose of the AZ vaccine should continue to be offered a second dose of AZ vaccine, irrespective of age. The second dose will be important for longer lasting protection against COVID-19.

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

Thrombotic events are known to occur in individuals with natural COVID-19 infection and more than a fifth of hospitalised patients with COVID-19 have evidence of blood clots. A study based on analysis of US data showed that CVST was a complication of COVID-19 infection, with a higher incidence (42.8 per million) compared to a matched cohort of patients with influenza (RR=2.67, 95% CI 1.04-6.81, P=0.031) and people who had received an mRNA vaccine ((RR=6.33, 95% CI 1.87–21.40, P=0.00014). However, this particular combination of thrombotic events and thrombocytopaenia is extremely rare and not known to be a common feature of COVID-19 infection. Based on cases reported to MHRA as of 4 August 2021, the overall incidence following the AZ vaccine is estimated at 14.9 per million first or unknown doses administered. For the latest information please see the weekly summary from the MHRA.

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

As of 11 August 2021, of the 412 suspected cases reported to the MHRA following the AZ vaccine, only a very small number of cases have been reported after the second dose. The JCVI concluded that there continues to be no safety concerns following the second dose of vaccine. As the number of second doses administered has increased, the much lower rate of reported cases after the second dose is reassuring, particularly for younger recipients where the incidence is significantly lower after the second dose compared to the first. Overall, there is no evidence of an increased risk after the second dose in any group.

The JCVI advises that those who have received their first dose of AZ vaccine should continue to be offered the second dose unless they have developed this specific syndrome of thrombosis and thrombocytopaenia following the first dose or have had an anaphylactic reaction. The Green Book has further information on contraindications to COVID-19 vaccines.

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. Although, the reported incidence rate is higher in females compared to males, this is not seen across all age groups and the difference remains small.

It is worth noting that more females were vaccinated early on in the programme, 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. 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.

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 is available here with specific guidance produced for Emergency Departments and Acute Medical Units and primary care.

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 a patient presents with symptoms suggestive of a blood clot in this time period please take the following actions:

Immediately refer patients to their local Emergency Department to have a Full Blood Count and further investigations carried out.

Report this case via the MHRA Yellow Card System (https://coronavirus-yellowcard.mhra.gov.uk).

At Emergency Departments, the standard Royal College of Emergency Medicine pathway should be followed and supportive guidance is available through local haematology teams for cases with confirmed thrombocytopaenia <150 x 10^9/l. Further guidance for secondary care is available here, with specific guidance for Emergency Departments and Acute Medical Units.

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://snapsurvey.phe.org.uk/snapwebhost/s.asp?k=161706705032 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://snapsurvey.phe.org.uk/snapwebhost/s.asp?k=161706705032.

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 contraindications to vaccination with the AZ vaccine include individuals who have a history of heparin induced thrombocytopaenia and thrombosis (HITT or HIT type 2). 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. Individuals who experience thrombosis with thrombocytopaenia following the first dose of the AZ vaccine should be properly assessed and if they are considered to have the reported condition, vaccination should be delayed until their clotting has completely stabilised and they should be considered for a second dose of an alternative COVID-19 vaccine. The Green Book has further information on contraindications and cautions to receiving the AZ vaccine.

Individuals aged 40 years or older 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 contraindicated). The same consideration applies to those who experience common clotting episodes, without concomitant thrombocytopaenia, after the first dose of AZ 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 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.

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 Organization and the European Medicines

Agency have concluded that the balance is very much in favour of vaccination. There are currently no safety concerns following receipt of the second dose of vaccine. There are no known risk factors for this extremely rare condition, which appears to be an idiosyncratic reaction on first exposure to the AZ vaccine. The JCVI advises that 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.

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 contraindications to vaccination with the AZ vaccine include individuals who have a history of heparin induced thrombocytopaenia and thrombosis (HITT or HIT type 2). These individuals may be offered vaccination with an alternative COVID-19 vaccine. Individuals who experience thrombosis with thrombocytopaenia following the first dose of the AZ vaccine should be properly assessed and if they are considered to have the reported condition, vaccination should be delayed until their clotting has completely stabilised and they should be considered for a second dose of an alternative COVID-19 vaccine. There is no evidence that those with a prior history of thrombosis or known risk factors for thrombosis, including antiphospholipid syndrome, are more at risk of developing this immune-mediated condition of thrombosis in combination with thrombocytopaenia after the AZ vaccine.

The Green Book has further information on contraindications and cautions to receiving the AZ vaccine.

Individuals over 40 years or older 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 contraindicated). The same consideration applies to those who experience common clotting episodes, without concomitant thrombocytopaenia, after the first dose of AZ 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 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.

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

A revision to the COVID-19 Green book chapter is available with updated information on cautions and contraindications for the AZ vaccine.

17. Can a patient with antiphospholipid syndrome have the vaccine?

Antiphospholipid syndrome increases the risk of thrombosis but 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 AZ vaccine. If an individual with antiphospholipid syndrome is aged 40 years or older and has no contraindications to the AZ vaccine, then they can receive the AZ vaccine.

This information is consistent with the JCVI's advice. The MHRA's current advice is that the AZ vaccine should be considered in individuals with antiphospholipid syndrome when the benefits of the vaccine outweigh the risk of that individual. The JCVI has reviewed the evidence on risks and benefits and has provided advice to the UK population on who should continue to be offered the AZ vaccine and this is the advice, as outlined in the Green Book, that should be followed for vaccination decisions.

For the majority of individuals, the risk of recurrent thrombosis due to COVID-19 infection is far greater than the risk of this syndrome following vaccination with AZ. Individuals who experience a clotting episode with concomitant

thrombocytopaenia following the first dose of the AZ 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. The contraindications to vaccination with the AZ vaccine include individuals who have a history of heparin-induced thrombocytopaenia and thrombosis (HITT of HIT type 2). These individuals may be offered vaccination with an alternative COVID-19 vaccine. Please see the Green Book for further advice on cautions and contraindications to vaccination.

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

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

The contraindications to vaccination with the AZ vaccine include individuals who have a history of heparin induced thrombocytopaenia and thrombosis (HITT or HIT type 2). These individuals may be offered vaccination with an alternative COVID-19 vaccine. Individuals who experience thrombosis with thrombocytopaenia following the first dose of the AZ vaccine should be properly assessed and if they are considered to have the reported condition, vaccination should be delayed until their clotting has completely stabilised and they should be considered for a second dose of an alternative COVID-19 vaccine. The Green Book has further information on contraindications and cautions to receiving the AZ vaccine. Individuals with bleeding disorders can still be vaccinated and further information is available in the Green Book.

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

Individuals who experience thrombosis with thrombocytopaenia following the first dose of the AZ vaccine should be properly assessed and if they are considered to have the reported condition, vaccination should be delayed until their clotting has completely stabilised and they should be considered for a second dose of an alternative COVID-19 vaccine (see the Green Book).

20. Can my patient still have a second dose of 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 contraindications to vaccination with the AZ vaccine include individuals who have a history of heparin induced thrombocytopaenia and thrombosis (HITT or HIT type 2). 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. Individuals who experience thrombosis with thrombocytopaenia following the first dose of the AZ vaccine should be properly assessed and if they are considered to have the reported condition, vaccination should be delayed until their clotting has completely stabilised and they should be considered for a second dose of an alternative COVID-19 vaccine.

The Green book has further information on contraindications and cautions to receiving the AZ 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 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. Individuals who experience a clotting episode WITH concomitant thrombocytopaenia following the first dose of AZ 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 1,000 people are affected by venous thrombosis each year. This compares with reports up to 19 May to the MHRA of 332 thrombosis events with low platelets out of a total of 24.2 million first doses of 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.

21. What if somebody under 40 years has had AZ for their first dose – should they have the second?

The AZ vaccine should continue to be offered to those in priority groups who have not yet been offered the vaccine. This includes older adults, those with underlying conditions, health and social care workers 40 years or older. 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 vaccine.

Those who have received their first dose of AZ vaccine and have not suffered this rare side-effect should continue to be offered the second dose to complete the course. Individuals aged 18 to 39 years who have received their first dose of AZ vaccine, without suffering this rare side effect, should complete their course with the same vaccine. This will include those who are eligible as part of the initial priority groups, such as health and social care workers, unpaid carers and family members of those who are immunosuppressed.

Whilst there is some evidence on the interchangeability of the COVID-19 vaccines and further studies are underway, it is recommended that individuals complete their initial COVID-19 vaccine course (doses 1 and 2) with the same vaccine, unless they have suffered this very rare side effect.

Data from two studies, one of 463 participants randomly assigned to different vaccine schedules and another of real world data of 1,313 participants, suggests that individuals receiving mixed schedules (a dose of AZ followed by a dose of Pfizer/BioNTech or vice versa) have higher rates of reactions.

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.

22. Should my patient have a second dose of a different vaccine other than the AZ vaccine?

Individuals who experience thrombosis with thrombocytopaenia following the first dose of the AZ vaccine should be properly assessed and if they are considered to have the reported condition, vaccination should be delayed until their clotting has completely stabilised and they should be considered for a second dose of an alternative COVID-19 vaccine. There are currently no safety concerns following receipt of the second dose of the AZ vaccine. This extremely rare condition appears to be an idiosyncratic reaction on first exposure to the AZ vaccine and there are no known risk factors for it. The JCVI advises that those who have received their first dose of the AZ vaccine without suffering this rare side effect should continue to be offered the second dose to complete the course. This includes individuals aged 18 to 39 years who have received their first dose of the AZ vaccine without this rare side effect.

Whilst there is some evidence on the interchangeability of the COVID-19 vaccines and further studies are underway, it is recommended that individuals complete their initial COVID-19 vaccine course (doses 1 and 2) with the same vaccine, unless they have suffered this very rare side effect. There is evidence that individuals receiving mixed schedules (a dose of AZ followed by a dose of Pfizer/BioNTech or vice versa) have higher rates of reactions. Therefore, every effort should be made to determine which vaccine the individual received and to complete with the same vaccine. Preliminary data from a study of 463 people aged 50 to 69 years in evaluating the interchangeability of COVID-19 vaccines suggests that a mixed schedule appears to lead to more systemic side effects after the second dose, such as fever and muscle aches. More individuals who received the AZ vaccine for the first dose and Pfizer/BioNTech for the second dose reported fever compared to those who received the AZ vaccine for both doses (difference 24%, 95% CI 13 to 35%). A similar pattern was seen for those individuals who received the Pfizer/BioNTech vaccine for both doses (difference 21%, 95% CI 8 to 33%).

Please see the Green Book for further advice on vaccination.

Real world data from a study of 1,313 individuals demonstrated that those who received mixed schedules had higher rates of reactions and sought medical attention more than those who had the same vaccine for both doses. In those individuals previously uninfected, the reaction rates for those receiving AZ then Pfizer/BioNTech were 54.4% ((5% CI; 28 to 39.2%) and for those receiving two doses of Pfizer/BioNTech, the reaction rates were 33.3% (95% CI 23.4 to 44.5%). Similar results were seen in those who had previously been infected with COVID-19.

23. 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 thrombocytopaenia 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.

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

Resources, such as patient information leaflets, have been produced which explain the benefits and risks of the AZ vaccination by different age bands. Older age groups, such as those aged 50 or older or with underlying medical problems, have a higher risk of hospitalisation, intensive care admission or death from COVID-19 infection than younger age groups:

- for those aged 50 and older or with underlying medical problems, the risk of this very rare side effect is around 1 in every 100,000 first doses and the benefit of one dose of the vaccine is an 80% reduction in deaths, hospitalisation and intensive care admission
- for people aged 40–49, the risk of this very rare side effect is around 1 in every 100,000 first doses and the benefit of one dose of the vaccine is 60 – 70% reduction in catching and passing on the infection
- for people aged 18–39, the risk of this very rare side effect is around 1 in every 50,000 first doses and the benefit of one dose of the vaccine is 60%–70% reduction in catching and passing on the infection

Someone who is vaccinated will continue to accrue benefits from the vaccination in the longer term by being protected against COVID-19, whilst the risk of vaccination occurs only in the few weeks after vaccination.

25. 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 40 years, an alternative vaccine will become available, but they may need to go to a different vaccination site. Resources, including patient leaflets, are available to support decision making.

26. What if my patient under 40 years old wants to have the AZ vaccine?

Patients under 40 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. Resources, including patient leaflets, are available to support decision making.

27. Can patients taking the combined oral contraceptive pill have the AZ vaccine?

Yes, patients taking the combined oral contraceptive pill can have the AZ vaccine, if they do not have any of the contraindications or cautions to its use (see the Green Book for further information).

The JCVI has concluded that for adults under 40 years of age who are not in a clinical risk group, it is preferable to offer an alternative to the AZ vaccine if available. Healthy adults aged 40-50 years are recommended to receive any of the available COVID-19 vaccines. 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.

Patients who are taking the combined oral contraceptive pill may be concerned that they have an increased risk of thrombosis and should not have the AZ 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 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. The Faculty of Sexual and Reproductive Healthcare have published a statement on this topic.

28. What is the current advice for pregnant women?

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 AZ vaccine. Hence, prothrombotic states such as pregnancy and contraception are not likely to confer a higher risk. However, because of more extensive experience and available safety data for Pfizer and Moderna vaccines from the USA, these vaccines are preferred in pregnancy. Further information is available in the Green Book.

29. What investigations do I need to organise for cases?

If a patient presents with symptoms suggestive of a blood clot in this time period please take the following actions:

Immediately refer patients to their local Emergency Department to have a Full Blood Count and further investigations carried out.

Report this case via the MHRA Yellow Card System (https://coronavirus-yellowcard.mhra.gov.uk).

At Emergency Departments, the standard Royal College of Emergency Medicine pathway should be followed and supportive guidance is available through local haematology teams for cases with confirmed thrombocytopaenia <150 x 10^9/l. Further guidance for secondary care is available here, with specific guidance for Emergency Departments and Acute Medical Units.

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://snapsurvey.phe.org.uk/snapwebhost/s.asp?k=161706705032 with details of the clinical presentation, dates of vaccination, vaccine product received and any underlying conditions.

Sources

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COVID-19 vaccine surveillance reports www.gov.uk/government/publications/covid-19-vaccine-surveillance-report

Vaccination, helping to protect those most vulnerable.

Information correct at time of publication. For the latest version of this factsheet, visit the PHA website **www.publichealth.hscni.net/publications**

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