ROYAL COLLEGE OF PHYSICIANS OF IRELAND

National Immunisation Advisory Committee

RECOMMENDATIONS
FOR THE USE OF VAXZEVRIA® COVID-19 VACCINE ASTRAZENECA

NIAC | 12.04.2021

Executive summary

All the authorised COVID-19 vaccines are highly effective in preventing hospitalisation and severe COVID-19 disease. Despite our falling case numbers, we remain in a pandemic that has claimed over 4,700 lives thus far in Ireland. The potential risk of any vaccine-associated harm must be balanced against the disease risk and alternative mitigation strategies, including the availability of other vaccines. Any delay in the national vaccination programme may increase the risk of severe disease and death in the most vulnerable.

The European Medicines Agency (EMA) has recently concluded an investigation into a number of reports of very rare, unusual blood clots occurring with low platelets in people following vaccination with Vaxzevria® COVID-19 Vaccine AstraZeneca. The EMA has added these unusual clotting events with low platelet counts as very rare side effects to the product information.

This event is estimated to occur between 4 and 10 in every 1 million people, one of whom may die. However, as so few events have been reported, there is a high level of uncertainty regarding the incidence of this extremely rare adverse event in any particular age group or gender.

Although most cases occurred in women under 60 years of age, this may be because of the higher rate of vaccination in healthcare workers who are predominantly female. In the UK the reported rate of events adjusted by sex and vaccination status was similar in men and women. A UK suggestion of a possible increasing incidence of this adverse event in the younger age groups has not been confirmed based on available European Economic Area (EEA) data. The EMA has requested new studies and amendments to ongoing ones to provide more information.

The risk/benefits of Vaxzevria® may vary by age. As alternative COVID-19 vaccines are available NIAC has revised the recommendations for use of this vaccine.

- Any authorised COVID-19 vaccine, including Vaxzevria®, is recommended for those aged 60 years and older including those with medical conditions with very high or high risk of severe COVID-19 disease
- Vaxzevria® is not recommended for those aged under 60 years including those with medical conditions with very high or high risk of severe COVID-19 disease
- A second dose of Vaxzevria® should not be given to anyone who developed unusual blood clots with low platelets after the first dose
- Those who have received a first dose of Vaxzevria®
    - Aged 60 and older should receive their second dose 12 weeks later as scheduled
    - Aged under 60 years
        - **with** a very high risk or high-risk medical condition should receive their second dose 12 weeks later as scheduled
        - **without** a very high risk or high-risk medical condition should have the scheduled interval between doses extended to 16 weeks to allow further assessment of the benefits and risks as more evidence becomes available

Introduction

On 7 April 2021, the EMA concluded its investigation into serious, very rare thromboembolic (clotting) events, typically complicated by thrombocytopenia (low platelet count) in adults under 60 years of age after vaccination with COVID-19 Vaccine AstraZeneca®, now called Vaxzevria®.

This document presents updated evidence relating to the safe use of Vaxzevria® and provides advice in respect of the use of this vaccine in Ireland.

Background

A combination of thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with Vaxzevria®. This includes severe cases presenting as venous thrombosis, including clotting at unusual anatomical sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis, with concomitant thrombocytopenia (associated low platelet count).

Following notification by the Health Products Regulatory Authority (HPRA) of a safety alert related to these clotting with low platelet events in adults after vaccination with Vaxzevria® in Europe, the National Immunisation Advisory Committee (NIAC) recommended a precautionary, temporary deferral of the administration of the vaccine on 14 March 2021.

On 18 March 2021 the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) reported its preliminary review. It was said that the vaccine was not associated with an increase in the overall risk of blood clots of all types in those who receive it, with around 20 million doses of Vaxzevria® had been administered within the UK and EEA. However, the vaccine may be associated with very rare cases of blood clots associated with low levels of blood platelets, and this deserved further analysis. The EMA confirmed that the benefits of the Vaxzevria® outweighed the risk of side effects.

On 19 March 2021, the National Immunisation Advisory Committee (NIAC) recommended the recommencement of the administration of Vaxzevria®. The PRAC continued to investigate further and involved experts in haematological disorders and other health authorities including the UK's Medicines and Healthcare products Regulatory Agency (MHRA).

On 7 April 2021, the EMA, MHRA, Joint Committee on Vaccination and Immunisation (JCVI) and WHO issued updated advice following the conclusions of their safety reviews. The EMA revised the EU product information to include the occurrence of "unusual blood clots with low blood platelets should be listed as very rare side effects" of the Vaxzevria®. All agencies noted the very low numbers of these reported events overall and acknowledged the challenge in determining incidence and specific risk factors. They all reiterated the efficacy of Vaxzevria® in preventing COVID-19 and reducing hospitalisations and death.

As new data emerges, work is ongoing to further refine a case definition and diagnosis for this condition. As of 8 April 2021, no cases describing these unusual clotting with low platelet events have been notified to the HPRA. However, a small number of notified reports describe some clinical and blood parameters of relevance, and therefore, are of special interest.

Discussion

In determining the recommendations below, NIAC met on a number of occasions to review the available evidence, attended EU meetings and collaborated with the National Coagulation Centre, HPRA, HIQA, DOH and other national and international stakeholders.

All the authorised COVID-19 vaccines are highly effective in preventing hospitalisation and severe COVID-19 disease. Despite our falling case numbers, we remain amid a pandemic that has claimed over 4,700 lives thus far in Ireland. The potential risk of any vaccine associated harm must be balanced against the disease related risk, both to the individual and the community, while considering other disease mitigation strategies including the availability of other vaccines. Any delay in the national vaccination programme may increase the risk of severe disease and death in the most vulnerable.

The EMA reported their in-depth review of 62 cases of cerebral venous sinus thrombosis and 24 cases of splanchnic vein thrombosis reported in the EU drug safety database as of 22 March 2021, 18 of which were fatal. The cases came from spontaneous reporting mainly from the EEA and the UK, where over 25 million people had received the Vaxzevria®. Available evidence suggests these unusual clotting with low platelet events may occur in between 4 and 10 in 1 million people, usually within 14 days after the first dose of vaccine, with an estimated death rate of one in a million. Higher rates have been reported in Germany and some Scandinavian countries. Given these cases have recently emerged as well as the known limitations of spontaneous reports, there is currently a high level of uncertainty in estimates of the incidence. However, in light of the extremely low numbers of events reported relative to the tens of millions of doses administered, this is considered overall to be a very rare adverse event. On 4 April 2021, a total of 222 clotting events with about 34 million doses of Vaxzevria® administered had been reported to the EMA and are under investigation.

A causal relationship between the vaccine and the occurrence of very rare, unusual blood clots with low platelets is considered plausible but is not confirmed. The EMA has concluded that unusual blood clots with low blood platelets should be listed as very rare side effects of Vaxzevria®. They reiterated that healthcare professionals and people receiving the vaccine should remain aware of the possibility of these very rare events usually occurring within two weeks of vaccination (appendix 1).

Data available from the UK suggest increasing reporting of these events with decreasing age whereas the risks of severe COVID-19 disease increase with age. Although most cases occurred in women, it is unclear whether this is related to the higher rate of vaccination in healthcare workers who are predominantly female. In the UK, the reporting rate of events (number of cases adjusted by sex and vaccination status) was said to be similar in men and women.

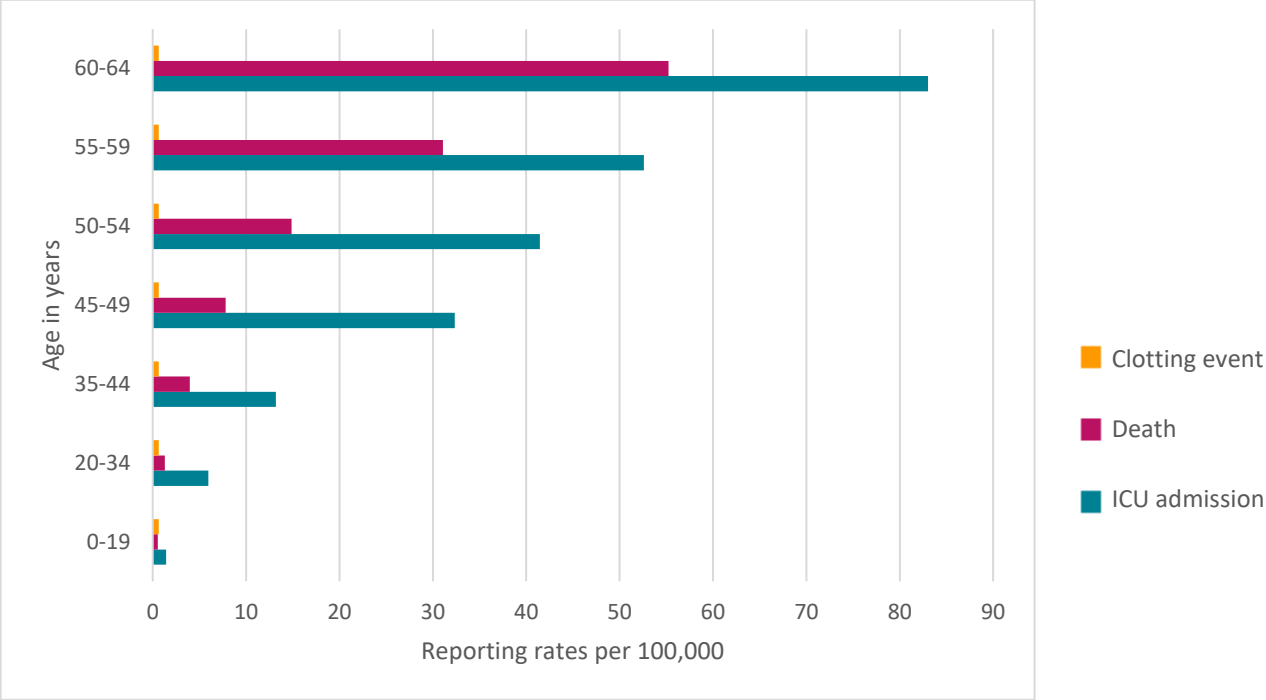
Based on the current evidence, no specific risk factors have been confirmed. There is no evidence of an increased risk for those with clotting or platelet disorders e.g. idiopathic or heparin induced thrombocytopenia, autoimmune conditions, history of cerebral venous sinus thrombosis, acquired or hereditary thrombophilia, or antiphospholipid syndrome.

Many European countries are currently experiencing a very significant increase in COVID-19 cases with subsequent increase in hospitalisations and deaths. This is in contrast with the UK where a higher proportion of the adult population has been vaccinated and lower levels of infection are being maintained. The current epidemiological position in Ireland is precarious with a high disease prevalence. Any delay in vaccination may increase the risk of severe disease and death in the most vulnerable.

All authorised vaccines can be used across all ages where the risk benefit ratio is favourable e.g. high risk of severe outcome from COVID-19, no alternative vaccines or mitigating strategies. In the UK, use of Vaxzevria® and Comirnaty® Pfizer/BioNTech COVID-19 vaccine in all adults with a prolonged interval between doses, in combination with public healthcare measures, has proven very effective in preventing COVID-19 related hospitalisation and deaths. This has also allowed for a substantial relaxation of public health restrictions and a reopening of their economy.

The table below shows that the rates of ICU admission and death from COVID-19 increase significantly with age. It also shows the rate of all clotting events reported up to 4 April 2021 to the EMA - 222 clotting events/34,000,000 people vaccinated - (0.65/100,000).

Table 1. Rates of COVID-19 related ICU admission and death per 100,000 population February 2020 – April 2021 and spontaneous reports of all clotting events (n = 222), EMA 4 April 2021



Source: Health Protection Surveillance Centre (HPSC) Computerised Infectious Disease Reporting (CIDR) extract 25.03.2021 Cases notified to Midnight 24.02.2021

Notes about the Table

Data for this table is based on the overall incidence rate for the ICU admission and death from COVID-19 in Ireland. This may underestimate the full burden of severe COVID-19 disease e.g. hospitalisation, long COVID or societal impact.

Conversely, the risk of harm from the vaccine may be overestimated as the 222 reports include all clotting events reported to the EMA as of 4 April, some yet to be fully investigated.

As age-specific data is not available from the EMA, this table assumes the same rate (0.65/100,000) across all age groups. This reporting rate (number of spontaneous reports notified/estimate of doses administered) has been included to illustrate the likelihood of a vaccine associated clotting event relative to the risk of severe COVID-19 disease and death (see Appendix 2).

HIQA analysis of risks associated with vaccination and COVID-19 infection

The purpose of the vaccination programme is to reduce the incidence of severe disease and death. The risk of harms due to COVID-19 infection are clearly related to the incidence of COVID-19.

The rates of infection have fluctuated substantially since March 2020. The benefit-harm balance was thus assessed for a variety of different incidence figures including periods of low and high infection rates. The estimated risk of the reported clotting events was weighed against the risk of death due to COVID-19.

In HIQA analysis, the age-specific risk of clotting events was inferred from UK data. In all scenarios considered, the benefits associated in giving Vaxzevria® to all those aged over 60 years exceeded the risks of any clotting event.

Vaccination of those who have already received one dose of Vaxzevria®

There are varying recommendations from other countries regarding the management of those who have already received one dose of Vaxzevria®.

NIAC is aware that some countries have recommended giving a mRNA vaccine instead of a second dose of Vaxzevria®. Clinical trials are ongoing of such schedules but NIAC has seen no evidence to support such a recommendation at this time.

Clinical trial data has shown that the Vaxzevria® is efficacious, with no waning of immunity, up to at least 12 weeks after the first dose. Data supports evidence of protective immunity for at least 16 weeks following a first dose of the vaccine.

Conclusion

Vaccination with Vaxzevria® is highly effective and substantially reduces the risk of severe COVID-19 disease across all age groups. NIAC were informed by the available scientific evidence and balanced the significant benefits of a national vaccination programme with the very rare risk of these reported events. While this is an extremely rare condition, consideration was given to the fact that it is has a very high risk of death or severe outcome. As the risk/benefits of Vaxzevria® may vary by age and as alternative COVID-19 vaccines are available NIAC has revised the recommendations for use of this vaccine.

Vaxzevria® can be used in adults aged under 60 years where the benefits clearly outweigh the risk for that individual and the person has made an informed decision based on an understanding of the risks and benefits.

New evidence will be reviewed once available and any further required amendments to recommendations notified to DOH.

Recommendations for the use of Vaxzevria®12 April 2021

This advice may be revised as more information becomes available or if the epidemiological situation changes.

Recommendation 1 Any authorised COVID-19 vaccine, including Vaxzevria®, is recommended for those aged 60 years and older, including those with medical conditions with very high or high risk of severe COVID-19 disease
Recommendation 2 Vaxzevria® is not recommended for those aged under 60 years, including those with medical conditions with very high or high risk of severe COVID-19 disease
Recommendation 3 A second dose of Vaxzevria® should not be given to anyone who developed unusual blood clots with low platelets after the first dose
Recommendation 4 Those who have received a first dose of Vaxzevria® ▪ Those aged 60 and older should receive their second dose 12 weeks later as scheduled ▪ Those aged under 60 years **- with** a very high risk or high-risk medical condition should receive their second dose 12 weeks later as scheduled **- without** a very high risk or high-risk medical condition should have the scheduled interval between doses extended to 16 weeks to allow further assessment of the benefits and risks as more evidence becomes available

Recommendations issued on 19 March 2021 remain unchanged

Healthcare professionals and vaccine recipients should be informed that very rare, complicated thromboembolic events have been reported in a small number of people who have recently received Vaxzevria®.
Healthcare professionals should be alert to the signs and symptoms of thromboembolism and/or thrombocytopenia and report any suspected adverse reactions to the HPRA.
Recipients of Vaxzevria® should be advised to seek immediate medical attention if they develop any of the following symptoms in the weeks after vaccination - shortness of breath, chest pain, leg swelling, persistent abdominal pain, neurological symptoms, such as severe and persistent headaches (particularly 3 or more days after vaccination) or blurred vision or tiny blood spots under the skin beyond the site of the injection.
Healthcare professionals should seek early expert advice from the National Coagulation Centre about the specialised testing and treatment options for patients presenting with thromboembolic events that are associated with thrombocytopenia, (including Disseminated Intravascular Coagulation (DIC) or Cerebral venous sinus thrombosis (CVST)) occurring within weeks following vaccination with Vaxzevria®.

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Appendix 1

Information for the general public

EMA statement

- Cases of unusual blood clots with low platelets have occurred in people who received Vaxzevria (formerly COVID-19 Vaccine AstraZeneca).
- The chance of having this occur is very low, but you should still be aware of symptoms so you can get prompt medical treatment to help recovery and avoid complications.
- You must seek urgent medical attention immediately if you have any of the following symptoms in the weeks after your injection:
    - shortness of breath
    - chest pain
    - leg swelling
    - persistent abdominal (belly) pain
    - neurological symptoms, such as severe and persistent headaches or blurred vision
    - tiny blood spots under the skin beyond the site of the injection.
- Speak to your healthcare professional or contact your relevant national health authorities if you have any questions about the roll out of the vaccine in your country.

Information for healthcare professionals

EMA statement

- EMA has reviewed cases of thrombosis in combination with thrombocytopenia, and in some cases bleeding, in people who received Vaxzevria (formerly COVID-19 Vaccine AstraZeneca).
- These very rare types of thrombosis (with thrombocytopenia) included venous thrombosis in unusual sites such as cerebral venous sinus thrombosis and splanchnic vein thrombosis as well as arterial thrombosis. Most of the cases reported so far have occurred in women under the age of 60 years. Most cases occurred within 2 weeks of the person receiving their first dose. There is limited experience with the second dose.
- As for the mechanism, it is thought that the vaccine may trigger an immune response leading to an atypical heparin-induced-thrombocytopenia like disorder. At this time, it is not possible to identify specific risk factors.
- Healthcare professionals should be alert to the signs and symptoms of thromboembolism and thrombocytopenia so that they can promptly treat people affected in line with available guidelines.
- Healthcare professionals should tell people receiving the vaccine that they must seek medical attention if they develop:
    - symptoms of blood clots such as shortness of breath, chest pain, leg swelling, persistent abdominal pain
    - neurological symptoms such as severe and persistent headaches and blurred vision
    - petechiae beyond the site of vaccination after a few days.
- The benefits of the vaccine continue to outweigh the risks for people who receive it. The vaccine is effective at preventing COVID-19 and reducing hospitalisations and deaths.
- National authorities may provide additional guidance on the roll out of the vaccine based on the situation in your country.

Appendix 2

Table. Rate of ICU admission, death from COVID-19 and reported clotting events after Vaxzevria® administration

Age group (in years)	Rates per 100,000			Likelihood of death from disease v adverse clotting event
	ICU admission	Deaths	Reported Clotting events	
0-19	1.43	0.53	0.65	1
20-34	5.96	1.30	0.65	2
35-44	13.20	3.97	0.65	6
45-49	32.36	7.81	0.65	12
50-54	41.46	14.87	0.65	23
55-59	52.61	31.09	0.65	48
60-64	83.04	55.23	0.65	85

Notes on the Table

Data for this table is based on the overall incidence rate for the ICU admission and death from COVID-19 in Ireland. This may underestimate the full burden of severe COVID-19 disease e.g. hospitalisation, long COVID or societal impact.

Conversely, the risk of harm from the vaccine may be overestimated as the 222 reports include all clotting events reported to the EMA as of 4 April, some yet to be fully investigated.

As age-specific data is not available from the EMA, this table assumes the same rate (0.65/100,000) across all age groups. This reporting rate (number of spontaneous reports notified/estimate of doses administered) has been included to illustrate the likelihood of a vaccine associated clotting event relative to the risk of severe COVID-19 disease and death.

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- Department of Health statisticians
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- Health Information and Quality Authority
- NIAC members
- RCPI Communications Department

About NIAC

NIAC includes representatives from Department of Health, HSE, the National Immunisation Office, the Irish College of General Practitioners (ICGP) the Health Protection Surveillance Centre (HPSC), the National Virus Reference Laboratory (NVRL UCD), representatives from the Faculties and Institutes of the Royal College of Physicians of Ireland, RCSI, the Infectious Diseases Society, the Nursing and Midwifery Board and representatives of the public. The Health Products Regulatory Authority (HPRA) also attend NIAC meetings to provide regulatory advice in relation to vaccines.

This group of experts meet to consider new evidence about vaccines and provide advice to the Chief Medical Officer and the Department of Health. The Department and the Minister for Health make policy decisions on vaccines which are implemented by the HSE.