ROYAL COLLEGE OF PHYSICIANS OF IRELAND

National Immunisation Advisory Committee

RECOMMENDATIONS FOR THE USE OF COVID-19 VACCINES
1. COVID-19 VACCINE JANSSEN
2. VAXZEVRIA COVID-19 VACCINE ASTRAZENECA
3. mRNA VACCINE DOSE INTERVAL

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About NIAC

NIAC includes representatives from the RCPI, its Faculties and Institutes, the RCSI, the ICGP, the National Immunisation Office, the Nursing and Midwifery Board of Ireland, the Infectious Diseases Society of Ireland, the Travel Medicine Society, the National Virus Reference Laboratory and lay members. Meetings are also attended by representatives from the Department of Health and the HSE, Representatives of the Health Products Regulatory Agency attend to provide regulatory advice in relation to vaccines.

NIAC meets 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.

Executive summary

These recommendations reflect a dynamic vaccination programme strategy. Scientific evidence about COVID-19 vaccines is continuously evolving and being refined. As in other countries, recommendations will be updated when more information becomes available.

NIAC considered the use of COVID-19 Vaccine Janssen and Vaxzevria® COVID-19 Vaccine AstraZeneca (now known as Vaxzevria®) with particular regard to their safety profile in light of the recent reports of unusual blood clots with low blood platelets, now known as Thrombosis Thrombocytopenia Syndrome (TTS).

TTS is a very rare side effect of Vaxzevria® and COVID-19 Vaccine Janssen®. At present, the nature of the risk for both vaccines is similar. There is uncertainty as to whether the risk of TTS is greater for one compared with the other. While more evidence is being collated similar recommendations have been made for these two vaccines.

All the authorised COVID-19 vaccines are highly effective in preventing hospitalisation and severe COVID-19 disease and the benefits of use outweigh the risks for all ages.

The benefit/risk ratio of the Vaxzevria® and COVID-19 Vaccine Janssen® vaccines is favourable in all ages and very clearly demonstrated in those aged 50 years and older, even when virus circulation is reducing in the community. Analysis of the benefit/risk ratio based on further EMA data clearly shows that these vaccines are appropriate for those aged 50 and older.

Most cases of TTS occurred in those aged under 50 years. 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. As the risks of TTS may be higher in younger adults and as alternative COVID-19 vaccines are available, NIAC has recommended the use of mRNA vaccines for those aged under 50 years.

There is insufficient evidence to support extending the interval beyond the recommended four weeks between the first and second dose of the mRNA COVID-19 vaccines.

In developing these recommendations, NIAC considered multiple factors including the risks of COVID-19 disease, the characteristics and the benefits of the vaccines, attended EU and the US Advisory Committee on Immunization Practices (ACIP) meetings, engaged with the National Coagulation Centre, HPRA, HIQA, DOH, HSE Social Inclusion, the High Level Task Force and other national and international stakeholders.

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

NIAC recommendations for COVID-19 vaccination 26.04.2021

Recommendations on the use of COVID-19 Vaccine Janssen®

- The overall benefits of COVID-19 vaccine Janssen® outweigh the risks
- Any authorised COVID-19 vaccine, including COVID-19 vaccine Janssen® is recommended for those aged **50 years and older** including those with medical conditions with very high or high risk of severe COVID-19 disease
- As alternative vaccines are available, mRNA vaccines are recommended for those aged **under 50 years** including those with medical conditions with very high or high risk of severe COVID-19 disease. In circumstances where a two-dose mRNA vaccination schedule is not a feasible alternative for those aged 18 – 49 years, the single dose COVID-19 vaccine Janssen® can be considered.

Recommendations on the use of Vaxzevria® COVID-19 Vaccine AstraZeneca

- The overall benefits of Vaxzevria® outweigh the risks
- Any authorised COVID-19 vaccine, including Vaxzevria®, is recommended for those aged **50 years and older** including those with medical conditions with very high or high risk of severe COVID-19 disease
- As alternative vaccines are available, mRNA vaccines are preferable for those aged **under 50 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 **50 and older** should receive their second dose 12 weeks later as scheduled. A shorter interval of 4 - <12 weeks may be used in exceptional circumstances
    - aged **under 50 years** with a very high risk or high risk medical condition should receive their second dose 12 weeks later as scheduled
    - aged **under 50 years** without a very high risk or high risk medical condition should have their second dose scheduled at 16 weeks, pending the availability of further evidence to permit better assessment of the benefits and risks. However, there may be others aged under 50 years who, fully informed of the very rare risk and symptoms of unusual blood clots and low platelets, wish to receive their second dose after 12 weeks and they should be facilitated where feasible.

Recommendations on the dose interval for mRNA vaccines

There is no change to the recommended interval of four weeks between the two doses of Comirnaty® Pfizer/ BioNTech or COVID-19 Vaccine Moderna® mRNA vaccines.

1.0 Introduction

On 21 April 2021, NIAC received a request from the Department of Health (DOH) to consider the use of COVID-19 Vaccine Janssen and Vaxzevria® COVID-19 Vaccine AstraZeneca (now known as Vaxzevria®) with particular regard to their safety profile in light of the recent EMA statements and to consider the comparative effectiveness of these vaccines.

On 12 April 2021 NIAC issued revised recommendations for use of Vaxzevria® in Ireland following the EMA safety committee (PRAC) conclusions that a warning about unusual blood clots with low blood platelets should be added to the vaccine's product information. On 20 April 2021, PRAC concluded that these events should be listed as very rare side effects for both vaccines.

Further information was issued on 23 April 2021 by the US Centers for Disease Control and Prevention (CDC) about COVID-19 Vaccine Janssen® and by the EMA about Vaxzevria®.

This document presents evidence relating to the safe use of COVID-19 Vaccine Janssen® and Vaxzevria® and provides advice in respect of the use of these vaccines in Ireland.

NIAC has also reviewed existing recommendations regarding the dosing interval of the COVID-19 mRNA vaccines.

The recommendations are developed in the context of an extremely dynamic situation where evidence to inform best practice is continually emerging. As in other countries, recommendations can be anticipated to change and be refined if and when it is warranted by the emerging evidence.

Thrombosis with Thrombocytopenia Syndrome

Cases of severe unusual clotting with low platelet count following Vaxzevria® were first noted in Europe in March 2021. The clinical features include clots at unusual sites such as the large veins, or sinuses, that drain the blood from the brain, called cerebral venous sinus thrombosis (CVST) and in blood vessels in the abdomen and at other sites. Similar events have been reported in the US in association with the COVID-19 Vaccine Janssen®. These are accepted as a very rare side effect of these vaccines.

This condition is now called Thrombosis with Thrombocytopenia Syndrome (TTS). A similar condition can occur very rarely in recipients of the blood thinning (anticoagulant) drug, Heparin. CVST and clots without low platelets can occur in the general population, however the biologic mechanism in these and other clots such as a deep vein thrombosis differs from that in TTS.

The risks associated with COVID-19 increase with age and are much greater than the risk of TTS associated with the vaccine. Clotting, including CVST, is a recognised complication of COVID-19. In the US, the incidence of CVST in those admitted to hospital within two weeks following COVID-19 is about 4 in 100,000. Approximately one in five patients admitted to ICU because of COVID-19 has clotting as a complication of COVID-19.

Conversely, the risk of TTS appears higher in younger age groups. These are the groups where risk of severe COVID-19 outcome is less, although the age-related risk of long-COVID is unknown.

Although more cases have been reported in females, this may reflect the fact that more women have been vaccinated. Some TTS cases have also been reported in men and further analysis is required to determine any sex-related risk.

No specific risk factors for TTS 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.

Early recognition and prompt treatment are important in the management of TTS. The initial pause of Vaxzevria® in Ireland allowed time for clinical treatment guidelines to be developed and widely disseminated (see appendix 1 and 2). This pause also allowed increased awareness of this condition, its recognition and appropriate management which has improved the outcome. However, TTS remains a condition of serious consequences that is potentially fatal.

Overall, the benefits of COVID-19 vaccination far outweigh the potential risks. The risk from COVID-19 is highest when there is a high level of virus transmission in the community. As the levels of virus circulating fall, so too does the risk that COVID-19 poses to the individual.

The Global Advisory Committee on Vaccine Safety recommends that *"countries assessing the risk of TTS following COVID-19 vaccination should perform a benefit-risk analysis that takes into account local epidemiology (including incidence and mortality from COVID-19 disease), age groups targeted for vaccination and the availability of alternative vaccines".*

Factors considered by NIAC when developing these recommendations

In determining the recommendations below, NIAC reviewed the available evidence, attended EU and the US Advisory Committee on Immunization Practices (ACIP) meetings, engaged with the National Coagulation Centre, HPRA, HIQA, DOH, HSE Social Inclusion, the High Level Task Force and other national and international stakeholders.

In forming any recommendations, NIAC weighs the potential risk of any vaccine associated harm against the known disease related risks, both to the individual and the community, while considering other disease mitigation strategies including the availability of other vaccines. In this pandemic situation, NIAC's overall priority for the vaccination programme continues to be prevention of severe disease and death in the most vulnerable and to reduce any barriers that might prevent individuals benefiting from the protection that vaccines afford.

2.0 COVID-19 Vaccine Janssen®

COVID-19 vaccine Janssen is a single dose adenovirus viral vector vaccine. In clinical trials, the vaccine reduced the risk of severe COVID-19 disease by 77% after 14 days, increasing to 85% after 28 days in those aged 18 and above. COVID-19 Vaccine Janssen® was authorised in the US on 27 February 2021 and vaccination commenced soon after. The vaccine was authorised in the EU on 11 March 2021. On 9 April 2021, the EMA announced a review of cases of TTS after COVID-19 Vaccine Janssen® that occurred in the US.

On 13 April 2021, the CDC and FDA recommended a pause in the use of COVID-19 Vaccine Janssen® pending the outcome of their investigation into these events and the distributor delayed the vaccine supply to Europe.

On 20 April 2021 the EMA reviewed US data and concluded that overall vaccine benefits outweigh the risk of side effects. A warning about TTS was added to the product information for COVID-19 Vaccine Janssen® and these events were listed as very rare side effects of the vaccine. This is similar as was listed for Vaxzevria®.

On 23 April 2021, the Advisory Committee on Immunization Practices (ACIP) in the US presented the evidence regarding TTS after COVID-19 Vaccine Janssen®. As of 21 April 2021, there were 15 confirmed TTS cases. The risk for TTS was estimated at 7 per million doses in females <50 years (highest in those aged 30 – 39 years) and <1 per million in females aged 50 and older and in males aged 18 years and older.

The recommendations of ACIP were informed by the threat of COVID-19 in the context of the continuing high disease transmission rates in the US, the known benefits of the COVID-19 Vaccine Janssen® and the unique benefit offered by a single dose vaccine.

The FDA determined that the available data show that the vaccine's known and potential benefits outweigh its known and potential risks in individuals 18 years of age and older. On 25 April 2021 the CDC recommended that the use of the COVID-19 Vaccine Janssen® should resume for all adults from age 18.

Recommendations remain under consideration in a number of other EU Member States. As of today, recommendations in the Netherlands and Germany have not set an age restriction, whereas in Spain, the vaccine use is initially restricted to those aged 70-79 years and older. France is restricting use to those aged 55 years and older.

3.0 Vaxzevria® COVID-19 Vaccine AstraZeneca

Vaxzevria® is a two-dose adenovirus viral vector vaccine. Following updated EU product information to include TTS as very rare side effects of Vaxzevria®, NIAC issued revised recommendations on 12 April 2021.

The vaccine was recommended for use in those aged 60 and older with those younger to be offered an alternative mRNA vaccine. As a two-dose vaccination schedule, recommendations were also made for those aged over 60 or who have a very high- or high-risk medical condition who have had a first dose to have their second dose after 12 weeks as scheduled. For all others, the interval was extended to 16 weeks to allow further assessment of the benefits and risks as more evidence becomes available.

On 23 April 2021 the EMA published further analysis of available data comparing the benefits of Vaxzevria® with the risk of TTS after the first vaccine dose for different age groups and different monthly rates of COVID-19 infection: low (55/100,000 people), medium (401/100,000 people) and high (886/100,000 people).

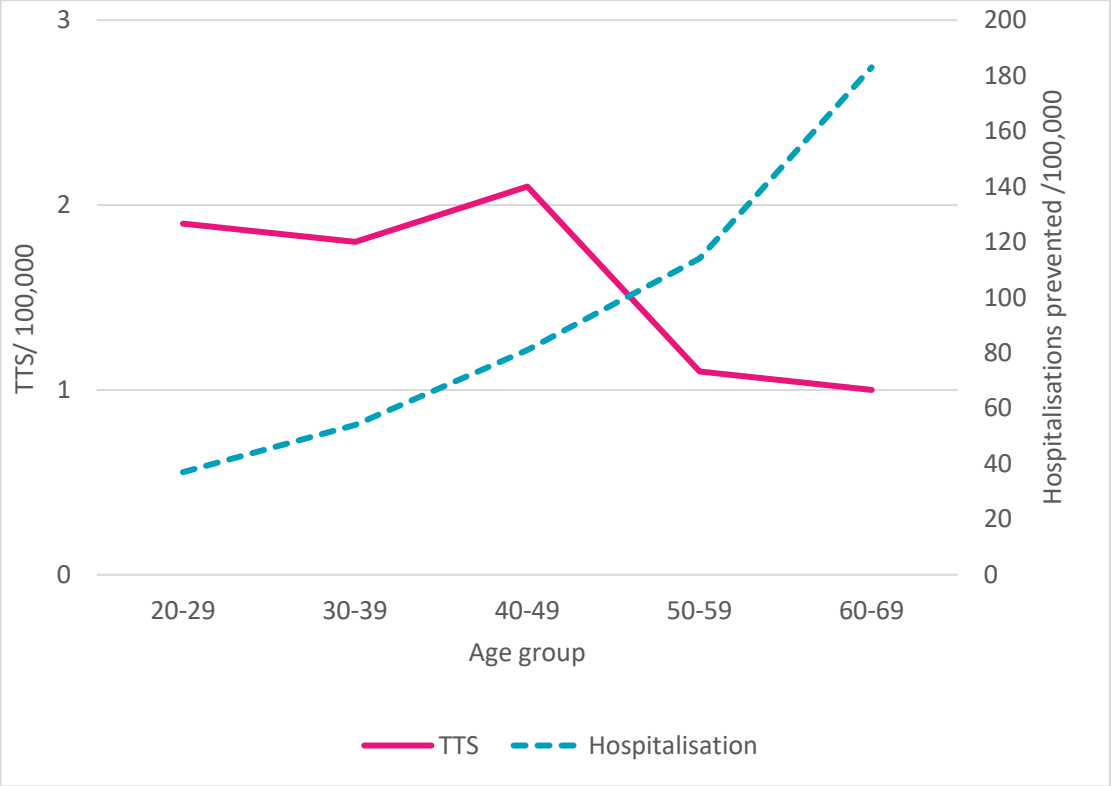
The risk of TTS appears higher in younger age groups. These are the groups where risk of severe COVID-19 outcome is less, although the age-related risk of long-COVID is unknown. The risk of TTS, estimated by the EMA (see appendix 3), varies from around 1 in 50,000 for age groups 20 – 49 years to 1 in 90,000-100,000 for those 50 – 70 years. Similar age-related risk has been reported in the UK.

Figure 1, derived from EMA data, illustrates the rate of COVID-19 hospitalisations prevented per 100,000 population compared to the risk of TTS following vaccination with Vaxzevria® in the context of medium exposure risk to COVID-19 disease. The current 14-day incidence rate of COVID-19 infection in Ireland is 117/100,000 between the medium and low incidence rates described by EMA.

The EMA analysis looked at prevention of hospitalisations, ICU admissions and deaths due to COVID-19, with the benefits of vaccination greatly outweighing the risk of TTS for those age 50 and older. The EU data were insufficient to allow comparison of the benefits and risks in males and females.

Figure 1. COVID-19 hospitalisations prevented with Vaxzevria® compared with TTS in the context of medium exposure

(*Note: graph for illustrative purposes only to show risk related to age. Left axis: TTS per 100,000. Right axis: hospitalisations prevented per 100,000*)



Source: EMA (2021) Annex to Vaxzevria Art.5.3 - Visual risk contextualisation https://www.ema.europa.eu/en/documents/chmp-annex/annex-vaxzevria-art53-visual-risk-contextualisation_en.pdf

The UK Medicines and Healthcare products Regulatory Authority (MHRA) reported 168 cases of TTS after 21.2 million doses of Vaxzevria®, a rate of 7.8 cases per million, with the data suggesting a higher rate reported in younger age groups.

In Ireland, by 19 April 2021, there have been 29 cases of thrombosis-like events reported to the HPRA following vaccination with Vaxzevria®. Less than five were associated with thrombocytopenia. The individuals concerned sought medical attention, received specialist medical care, as outlined above, and are reported to be responding well to treatment.

Vaccination of those who have received one dose of Vaxzevria®

Clinical trial data has shown that protection starts from approximately three weeks after the first dose of Vaxzevria® with 76% protection overall against symptomatic COVID-19 disease for up to 90 days. Modelling predicted no waning of protection in the first three months after vaccination. Higher efficacy of 82% was reported when the second dose was given after a longer interval of 12 weeks compared to a shorter interval of 4 weeks. Data supports evidence of protective immunity for at least 16 weeks following a first dose of the vaccine.

As yet, there is no evidence to support giving a mRNA vaccine instead of a second dose of Vaxzevria®.

In the UK, of 168 reported cases of TTS only one occurred after the second dose. To date, 2.3 million second doses have been given. Preliminary evidence suggests that the risk of TTS may be substantially lower (0.4 cases/million) after a second dose. Follow up is required to further define the associated risks.

Protection following Vaxzevria®

Three weeks after one dose of Vaxzevria® and COVID-19 vaccine Janssen ®, levels of protection against severe disease are comparable. Protection following one dose of Vaxzevria® persists for at least 12 weeks. However, all clinical trials and post marketing are based on a two-dose schedule of Vaxzevria® and the second dose is essential to enhance durability of protection. As for all COVID-19 vaccines the long-term duration of the immune response is unknown. There is insufficient evidence to allow a change from the authorised two-dose Vaxzevria® schedule.

4.0 Dose interval mRNA vaccines

NIAC undertook a comprehensive literature review of the evidence for the interval of a two-dose mRNA vaccine schedule. NIAC also considered available international dose interval recommendations. A sample of evidence reviewed is included in Appendix 4.

International recommendations

Canada: National Advisory Committee on Immunization (NACI)

"In the context of limited COVID-19 vaccine supply and ongoing pandemic disease, jurisdictions should maximize the number of individuals benefiting from the first dose of vaccine by extending the second dose of COVID-19 vaccine up to four months after the first. Second doses should be offered as soon as possible after all eligible populations have been offered first doses, with priority given to those at highest risk of severe illness and death from COVID-19 disease. Vaccinated people (with one or two doses) should continue to follow recommended public health measures. NACI will continue to monitor the evidence on effectiveness of an extended dose interval and will adjust recommendations as needed."

https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/extended-dose-intervals-covid-19-vaccines-early-rollout-population-protection.html

European Centre for Disease Prevention and Control (ECDC)

Some countries extended the timing between mRNA vaccine doses at the start of their vaccination programmes to provide the first dose to as many people in the priority groups as possible. Regarding the timing between first and second dose, policies vary by country and product as follows:

Comirnaty®	At least 3 weeks (Italy) 4 weeks (Ireland, Portugal), 6 weeks (Estonia, Norway, Croatia, the Netherlands, Poland) 12 weeks (Finland)
COVID-19 Vaccine Moderna	6 weeks (Norway 12 weeks (Finland)

https://www.ecdc.europa.eu/sites/default/files/documents/Overview-implementation-COVID-19-vaccination-strategies-vaccine-deployment-plans.pdf

UK: The Green Book

Comirnaty® "should be administered in two doses, a minimum of 21 days apart. Operationally, it is recommended that a consistent interval should be used for all vaccines to avoid confusion and simplify booking. Currently, a schedule of around 12 weeks is being followed to allow more people to benefit from the protection provided from the first dose during the roll out phase. Longer term protection will then be provided by the second dose."

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/978508/Green_book_chapter_16April2021.pdf

UK: Joint Committee on Vaccination and Immunisation (JCVI)

Given the high level of protection afforded by the first dose, models suggested that initially vaccinating a greater number of people with a single dose would prevent more deaths and hospitalisations than vaccinating a smaller number of people with 2 doses. The second dose is still important to provide longer lasting protection and is expected to be as or more effective when delivered at an interval of 12 weeks from the first dose.

Short-term vaccine efficacy from the first dose of Comirnaty® was calculated at around 90%. Short-term vaccine efficacy from the first dose of Vaxzevria® was calculated at around 70%, with high protection against severe disease.
https://www.gov.uk/government/publications/prioritising-the-first-covid-19-vaccine-dose-jcvi-statement/optimising-the-covid-19-vaccination-programme-for-maximum-short-term-impact

USA: Centers for Disease Control and Prevention (CDC)

"The second dose of Pfizer-BioNTech and Moderna vaccines should be administered as close to the recommended interval as possible, but not earlier than recommended (i.e., 3 weeks [Pfizer-BioNTech] or 1 month [Moderna]). However, second doses administered within a grace period of 4 days earlier than the recommended date for the second dose are still considered valid. If it is not feasible to adhere to the recommended interval and a delay in vaccination is unavoidable, the second dose of Pfizer-BioNTech and Moderna COVID-19 vaccines may be administered up to 6 weeks (42 days) after the first dose. Currently, only limited data are available on efficacy of mRNA COVID-19 vaccines administered beyond this window."
https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html

US Food and Drug Administration (FDA)

"At this time, suggesting changes to the FDA-authorized dosing or schedules of these vaccines is premature and not rooted solidly in the available evidence. Without appropriate data supporting

such changes in vaccine administration, we run a significant risk of placing public health at risk, undermining the historic vaccination efforts to protect the population from COVID-19."
https://www.fda.gov/news-events/press-announcements/fda-statement-following-authorized-dosing-schedules-covid-19-vaccines

World Health Organization (WHO)

"Countries experiencing exceptional epidemiological circumstances may consider delaying for a short period the administration of the second dose as a pragmatic approach to maximizing the number of individuals benefiting from a first dose while vaccine supply continues to increase. WHO's recommendation at present is that the interval between doses may be extended up to 42 days (6 weeks), on the basis of currently available clinical trial data.

Some countries have therefore considered delaying the administration of the second dose to allow for a higher initial coverage. This is based on the observation that efficacy has been shown to start from day 12 after the first dose and reached about 89% between days 14 and 21, at the time when the second dose was given. No data on longer term efficacy for a single dose of the mRNA vaccine BNT162b2 currently exist, as the trial participants received 2 doses with an interval between doses in the trial ranging from 19 to 42 days"
https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-BNT162b2-2021.1.

Summary of evidence for dose interval of mRNA vaccines

There is insufficient evidence to support extending the interval between the first and second dose of the mRNA COVID-19 vaccines, although modelling studies support extending the interval where disease transmission is high and vaccine supplies are limited. The follow up period in published studies relating to an extended interval is usually less than 35 days. Most studies did not address protection provided by the second or booster dose of vaccine against variants.

Some countries decided to delay the second vaccine dose at the start of their vaccination programme when vaccine supplies were limited and when there was widespread community transmission of COVID-19.

Evidence supports adhering to the recommended interval. This may be particularly important in those aged 65 and older and in those under 65 years with high risk medical conditions.

5.0 Conclusion

All the authorised COVID-19 vaccines are highly effective in preventing hospitalisation and severe COVID-19 disease and the benefits of use outweigh the risks for all ages.

TTS is a very rare side effect of Vaxzevria® and COVID-19 Vaccine Janssen®. At present, the nature of the risk for both vaccines is similar. There is uncertainty as to whether the risk of TTS is greater for one compared with the other. While more evidence is being collated similar recommendations have been made for these two vaccines.

The benefit/risk ratio of the Vaxzevria® and COVID-19 Vaccine Janssen® vaccines is favourable in all ages and very clearly demonstrated in those aged 50 years and older, even when virus circulation is reducing in the community. Most cases of TTS occurred in those aged under 50 years. Analysis of the benefit/risk ratio based on further EMA data clearly shows that these vaccines are appropriate for those aged 50 and older.

As the risks of TTS may be higher in younger adults and as alternative COVID-19 vaccines are available, NIAC has recommended the use of mRNA vaccines for those aged under 50 years.

There is insufficient evidence to support extending the interval beyond the recommended four weeks between the first and second dose of the mRNA COVID-19 vaccines.

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

Note re vaccine selection for immunocompromised persons

Immunocompromise may be associated with a suboptimal response to vaccines. As previously recommended, mRNA vaccines, with higher efficacy in clinical trials, might therefore be preferable for patients who are immunocompromised. However, if preferential selection of an mRNA vaccine will result in delayed vaccination for more than 3 weeks, any benefit of using a higher efficacy vaccine may be lost.

For further information, see National Immunisation Guidelines Chapter 5a COVID-19.

6.0 NIAC recommendations for COVID-19 vaccination 26.04.2021

Recommendations on the use of COVID-19 Vaccine Janssen®
• The overall benefits of COVID-19 vaccine Janssen® outweigh the risks • Any authorised COVID-19 vaccine, including COVID-19 vaccine Janssen® is recommended for those aged **50 years and older** including those with medical conditions with very high or high risk of severe COVID-19 disease • As alternative vaccines are available, mRNA vaccines are recommended for those aged **under 50 years** including those with medical conditions with very high or high risk of severe COVID-19 disease. In circumstances where a two-dose mRNA vaccination schedule is not a feasible alternative for those aged 18 – 49 years, the single dose COVID-19 vaccine Janssen® can be considered.

Recommendations on the use of Vaxzevria® COVID-19 Vaccine AstraZeneca

• The overall benefits of Vaxzevria® outweigh the risks
• Any authorised COVID-19 vaccine, including Vaxzevria®, is recommended for those aged **50 years and older** including those with medical conditions with very high or high risk of severe COVID-19 disease
• As alternative vaccines are available, mRNA vaccines are preferable for those aged **under 50 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 **50 and older** should receive their second dose 12 weeks later as scheduled. A shorter interval of 4 - <12 weeks may be used in exceptional circumstances
  ○ aged **under 50 years** with a very high risk or high risk medical condition should receive their second dose 12 weeks later as scheduled
  aged **under 50 years** without a very high risk or high risk medical condition should have their second dose scheduled at 16 weeks, pending the availability of further evidence to permit better assessment of the benefits and risks. However, there may be others aged under 50 years who, fully informed of the very rare risk and symptoms of unusual blood clots and low platelets, wish to receive their second dose after 12 weeks and they should be facilitated where feasible.

Recommendations on the dose interval for mRNA vaccines
There is no change to the recommended interval of four weeks between the two doses of Comirnaty® Pfizer/ BioNTech or COVID-19 Vaccine Moderna® mRNA vaccines.

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link-between-covid-19-vaccine-astrazeneca-and-extremely-rare-unlikely-to-occur-blood-clots

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Appendix 1

IRISH HAEMATOLOGY SOCIETY COAGULATION SPECIAL INTEREST GROUP (VERSION 1.0 DATED 16.4.21)

Guidance on diagnosis and management of thrombocytopenia and thrombosis associated with adenoviral vector COVID19 vaccination

Also known as:

Vaccine-induced immune thrombocytopenia (VITT)

Vaccine-Induced Prothrombotic Immune Thrombocytopenia (VIPIT)

1.0 Purpose/Scope

The aim of this guidance is to provide guidance to clinicians in relation to diagnosis and clinical management of patients who present with thrombocytopenia and/or thrombosis associated with adenoviral vector COVID19 vaccination.

2.0 Background

Coronavirus disease 2019 (COVID-19) is caused by the novel severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), which can lead to systemic multiorgan complications and an increased risk of both venous and arterial thromboembolism. Several vaccines have been rapidly developed and subsequently approved by regulatory agencies including the Irish Health Products Regulatory Agency (HPRA) and are in use in Ireland and throughout the world to address the impact of the COVID-19 pandemic.

The ChAdOx1 nCoV-19 vaccine (AZD1222, produced by AstraZeneca (Vaxzevria®)) has been associated with reports of unusual blood clots including cerebral vein and sinus thrombosis (CVST) and thrombosis at other unusual sites including splanchnic vein thrombosis, in conjunction with thrombocytopenia, elevated d-dimers and in some cases, hypofibrinogenaemia and bleeding [1-3]. A number of the reported cases had a fatal outcome. On 7th April 2021, the European Medicines Agency (EMA) safety committee (Pharmacovigilance Risk Assessment Committee (PRAC)) concluded that “unusual blood clots with low

blood platelets should be listed as very rare side effects of Vaxzevria (formerly COVID-19 Vaccine AstraZeneca)" [1]. It was noted that "as of 4 April 2021, a total of 169 cases of CVST and 53 cases of splanchnic vein thrombosis were reported to EudraVigilance. Around 34 million people had been vaccinated in the EEA and UK by this date." These rare events are estimated to occur between 4 and 10 in every 1 million people, one of whom may die[4].

3.0 Diagnosis

Patients presenting with the following symptoms 4-28 days after administration of the AstraZeneca (Vaxzevria®) COVID-19 vaccine should be investigated as a potential case of thrombocytopenia and/or thrombosis associated with adenoviral vector COVID19 vaccination.

- 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.

At present, it there is **no evidence** that patients with a history of thrombosis and/or known thrombophilia have an increased risk of developing this unusual and very rare complication after vaccination with the AstraZeneca (Vaxzevria®) COVID-19 vaccine.

Flulike symptoms such as joint and muscle pain or headache that persist for 1 to 3 days after vaccination are a common side effect and not a cause for concern.

CONSULT THE HAEMATOLOGY TEAM AT YOUR HOSPITAL IF A PATIENT PRESENTS WITH SYMPTOMS SUGGESTIVE OF VITT/VIPIT: The Haematology team will need to be aware of these suspected cases, will need to review the blood film and blood test results and advise on confirmatory testing and interim clinical management.

Send the following initial blood tests:

- FBC
- Blood film (to outrule other causes of thrombocytopenia)
- Coagulation screen
- Clauss Fibrinogen

- D-Dimers
- Biochemical profile
- LDH
- Lactate
- Antiphospholipid antibody screening (lupus anticoagulant, anticardiolipin and anti beta2 glycoprotein 1 antibodies), if available locally. If not available locally, send sample to the National Coagulation Laboratory (see below).

Imaging:

Imaging investigations should be ordered according to the presenting symptoms.

Imaging to rule out CVST includes both parenchymal imaging and vascular imaging, either with a CT brain/CT venogram, or MR brain/MR venogram.

Imaging for splanchnic vein thrombosis, if patients present with abdominal pain, should include a CT abdomen with contrast

Arterial thrombosis should be considered if patients have consistent symptoms.

4.0 Confirmatory laboratory testing

Confirmatory laboratory testing is similar to Heparin induced thrombocytopenia (HIT) testing. Please contact your local laboratory and arrange to send the following samples to the National Coagulation Laboratory (NCL), SJH:

4 serum (5mL samples)

2 plasma (3mL citrate samples)

Contact details

Routine hours (Monday-Friday 8am-8pm, Saturday 9am-1pm): 01-4162910/4162908

Out of hours: 01 4103000, bleep 671

N.B. Samples must be taken BEFORE Intravenous immunoglobulin (IVIg) is administered.

The following tests will be performed in the NCL:

- Diamed Platelet factor 4/heparin gel immunoassay (note that this test is usually negative in VITT/VIPIT)
- Immucor PF4 IgG Elisa (this test may be strongly positive in VITT/VIPIT)

- If the Elisa is positive, the sample will be sent to the laboratory of Prof Andreas Greinacher, Greifswald, Germany for confirmatory platelet activation assays.
- If required, the NCL will also perform testing for Lupus Anticoagulant and the Immunology laboratory in SJH will do tests for anticardiolipin and anti-beta 2 glycoprotein 1 antibodies to rule out antiphospholipid antibodies as a cause of immune thrombocytopenia.

5.0 Management

Initially, it may be difficult to make a confirmed diagnosis of VITT/VIPIT, while the clinical presentation may be evolving and the results of all laboratory tests are not yet available. However, if VITT/VIPIT is likely based on the clinical presentation and the available laboratory results, treatment should not be delayed.

VITT/VIPIT unlikely:

- Clinical symptoms requiring investigation (per section 3.0) with a normal platelet count, normal d-dimer and normal fibrinogen.
- Thrombosis with a normal platelet count and a normal fibrinogen.
- Reduced platelet count without thrombosis, normal d-dimer , normal fibrinogen

In these cases, investigations should proceed as per usual clinical practice.

Suspected VITT/VIPIT:

Confirmed thrombocytopenia (platelet count < 150 x 10^9/L) 4-28 days post AstraZeneca vaccine without other cause

Elevated d-dimers

+/- low fibrinogen

+/- thrombosis (CVST, splanchnic vein thrombosis, arterial thrombosis or other)

Confirmed VITT/VIPIT:

As for suspected VITT/VIPIT plus

PF4 IgG Elisa positive

+/-Platelet activation assay positive

Patients with suspected and confirmed VITT/VIPIT should be treated similarly to HIT and certain treatments should be avoided, as follows:

Treatments to avoid in suspected VITT/VIPIT
• **AVOID** all forms of heparin including heparin-based flushes, including low molecular weight heparin and fondaparinux in acute phase
• **AVOID** platelet transfusions
• **AVOID** thrombopoietin receptor agonists

Patients with suspected or confirmed VITT/VIPIT and thrombosis

Give IVIg 1g/kg x 2 days.

Give therapeutic anticoagulation, if Platelet count >30 x 10^9/L and Fibrinogen >1.5 g/L.

Options* include:

1. Therapeutic dose direct oral anticoagulant (DOAC)
2. IV Argatroban per protocol, target APTTr 1.5-3.0
    - For monitoring, ensure baseline APTT is below the upper limit of normal
    - Argatroban levels are available at the NCL if required, in discussion with the NCC Consultant on call
3. IV Danaparoid
    - For monitoring, anti-Xa levels are available at the NCL, in discussion with the NCC Consultant on call

If the fibrinogen level is <1.5g/L, consider replacement with Fibrinogen concentrate prior to therapeutic anticoagulation.

Consider Plasma exchange in severe cases as adjunct therapy.

Patients on IV anticoagulants can convert to therapeutic dose DOAC once clinically improved.

Duration of anticoagulation: 3 months, or longer if persistent VTE risk factors eg immobility.

*If patients are pregnant, choice of anticoagulant will be restricted to IV Argatroban or IV/SC Danaparoid.

Patients suspected or confirmed VITT/VIPIT without thrombosis

Consider IVIg 1g/kg x 2 days, particularly if there is evidence of a developing coagulopathy on serial monitoring.

Consider therapeutic anticoagulation, if Platelet count >30 x 10^9/L and Fibrinogen >1.5 g/L:

Options* include:

1. Therapeutic dose direct oral anticoagulant (DOAC)
2. IV anticoagulation with Argatroban or Danaparoid as outlined above

*If patients are pregnant, choice of anticoagulant will be restricted to IV Argatroban or IV/SC Danaparoid.

If the fibrinogen level is <1.5g/L, consider replacement with Fibrinogen concentrate.

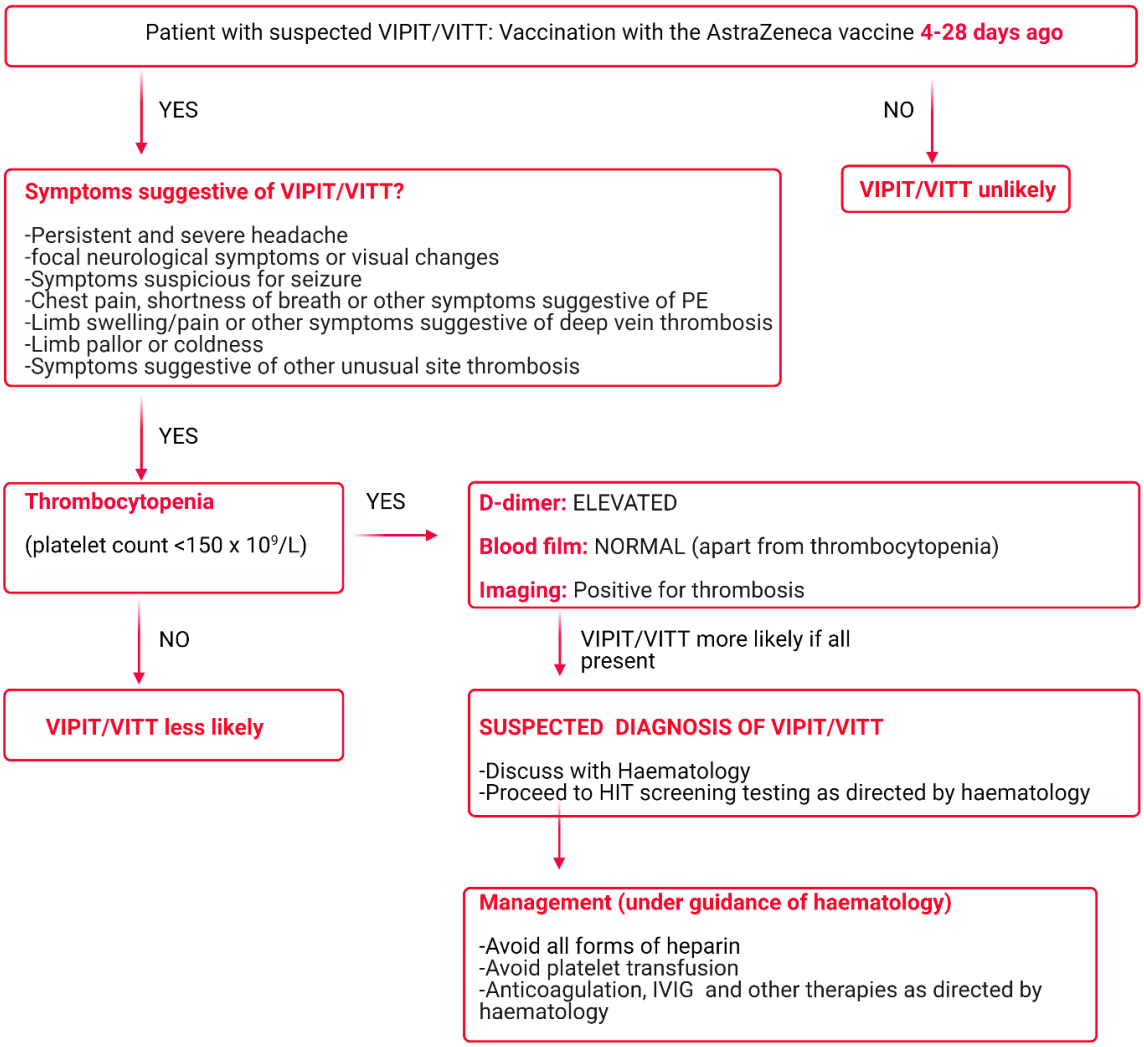
Duration of anticoagulation: 1 month, or longer if persistent VTE risk factors eg immobility.

6.0 Reporting Adverse Reactions

Report all suspected adverse reactions including thrombosis, and both presumptive and confirmed VIPIT, to the HPRA using the following link:

https://www.hpra.ie/homepage/about-us/report-an-issue/covid-19-vaccine-adverse-reaction

Figure 1: Approach to possible case of VITT/VIPIT



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8.0 Authorship

This guidance has been devised by the Irish Haematology Society Coagulation Special Interest Group.

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Prof. Fionnuala Ní Áinle, Mater Misericordiae University Hospital

Dr Beatrice Nolan, Children's Health Ireland, Crumlin

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Dr Denis O'Keeffe, Limerick University Hospital

Appendix 2

NIAC Recommendations issued 19 March 2021 remain unchanged and should be seen as applicable to both Vaxzevria® and COVID-19 Vaccine Janssen®

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®.

Appendix 3

EMA (2021) ANNEX TO VAXZEVRIA ART.5.3 - VISUAL RISK CONTEXTUALISATION 23.04.2021

https://www.ema.europa.eu/en/documents/chmp-annex/annex-vaxzevria-art53-visual-risk-contextualisation_en.pdf

Introduction

To support national authorities making decisions on how to best use the vaccine in their territories, EMA's human medicines committee (CHMP) has further analysed available data to put the risks of very rare blood clots (thrombosis with thrombocytopenia syndrome, TTS) in the context of the benefits for different age groups and different rates of infection.

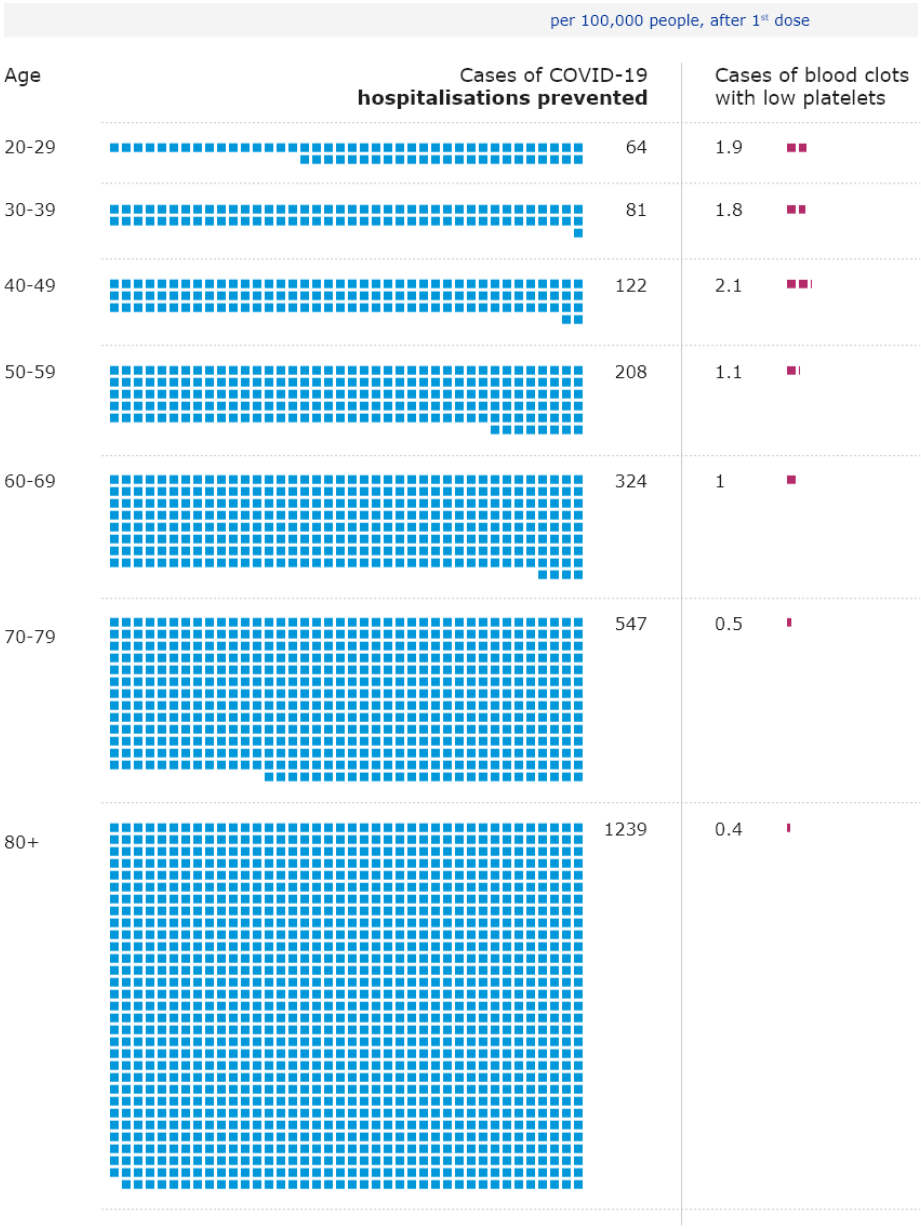
The analysis will inform national decisions on the roll out of the vaccine, taking into account the pandemic situation as it evolves and other factors, such as vaccine availability. The analysis could change as new data become available.

The Committee analysed the benefits and the risk of unusual blood clots with low platelets in different age groups in the context of the daily infection rate: low (55 per 100,000 people), medium (401 per 100,000 people) and high (886 per 100,000 people).

The analysis looked at prevention of hospitalisations, ICU admissions and deaths due to COVID-19, considering an 80% vaccine effectiveness over a period of four months. The details of the full analysis and methodology are available in the assessment report which will be published shortly.

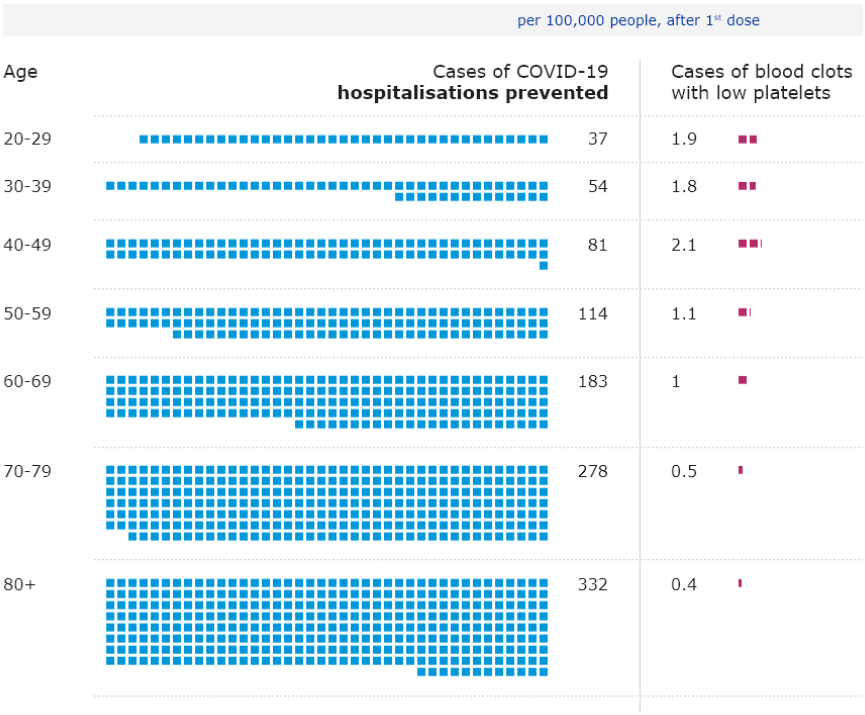
1. **COVID-19 hospitalisations prevented with Vaxzevria compared with unusual blood clots with low platelets**

High infection rate*



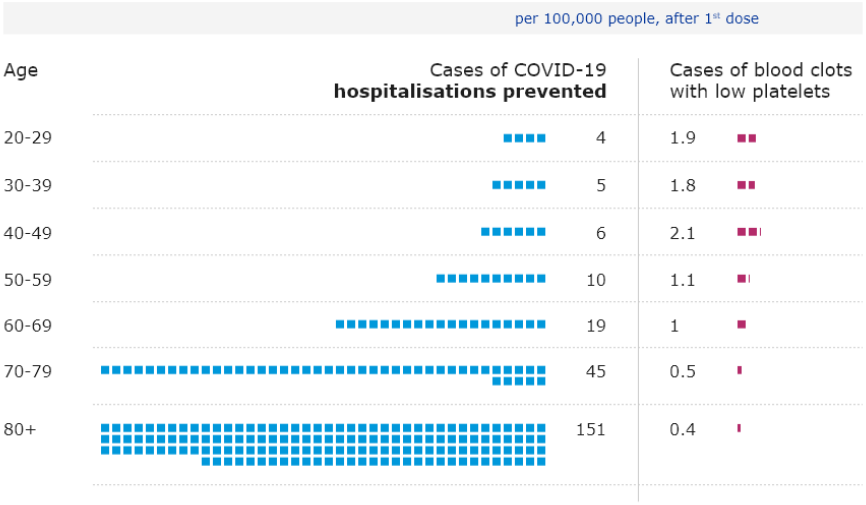
* "High" exposure: using virus circulation for January 2021 (incidence 886/100,000 population)

Medium infection rate*



* "Medium" exposure: using virus circulation for March 2021 (incidence 401/100,000 population)

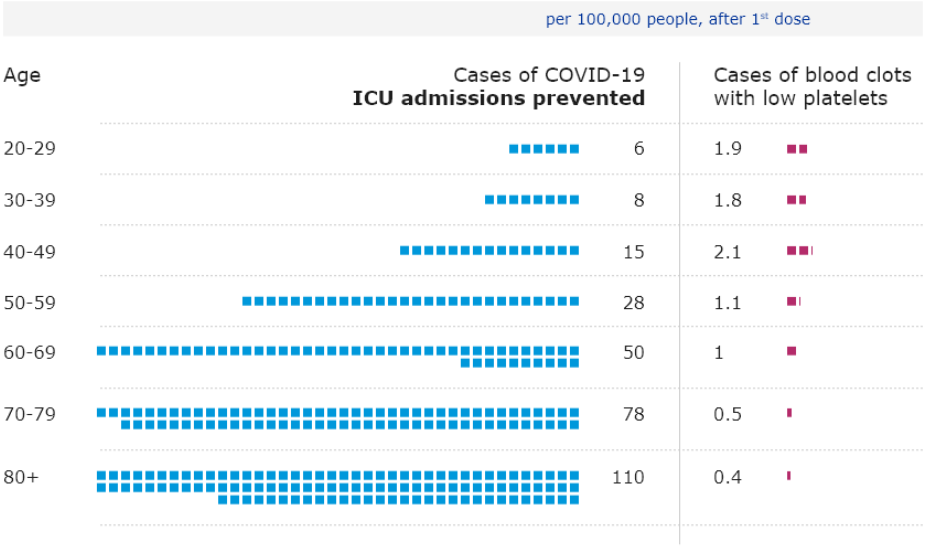
Low infection rate*



* "Low" exposure: using virus circulation for September 2020 (incidence: 55/100,000 population)

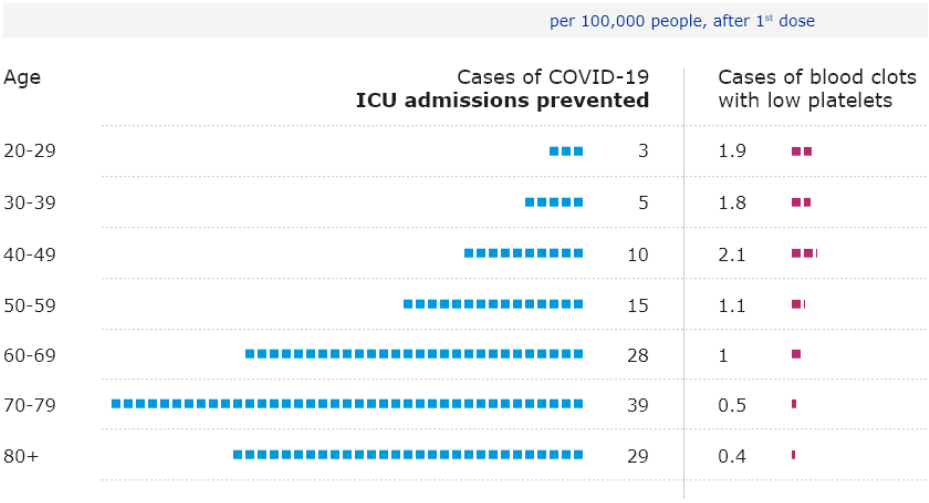
2. **COVID-19 ICU admissions prevented with Vaxzevria compared with unusual blood clots with low platelets**

High infection rate*



* "High" exposure: using virus circulation for January 2021 (incidence 886/100,000 population)

Medium infection rate*



* "Medium" exposure: using virus circulation for March 2021 (incidence 401/100,000 population)

Low infection rate*

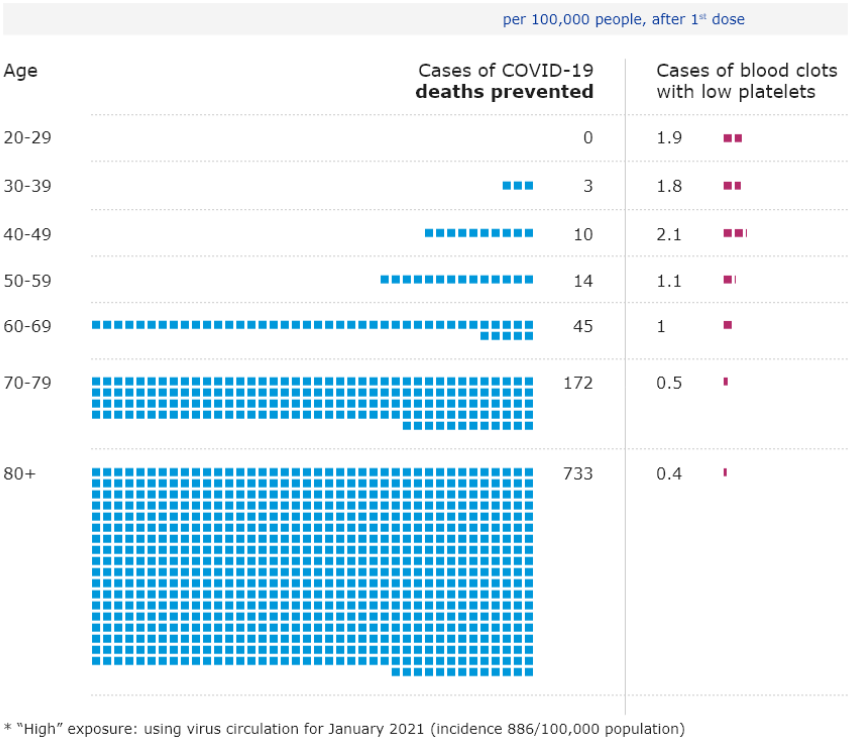
per 100,000 people, after 1st dose

Age	Cases of COVID-19 **ICU admissions prevented**	Cases of blood clots with low platelets
20-29	0	1.9
30-39	0	1.8
40-49	1	2.1
50-59	1	1.1
60-69	3	1
70-79	6	0.5
80+	13	0.4

* "Low" exposure: using virus circulation for September 2020 (incidence: 55/100,000 population)

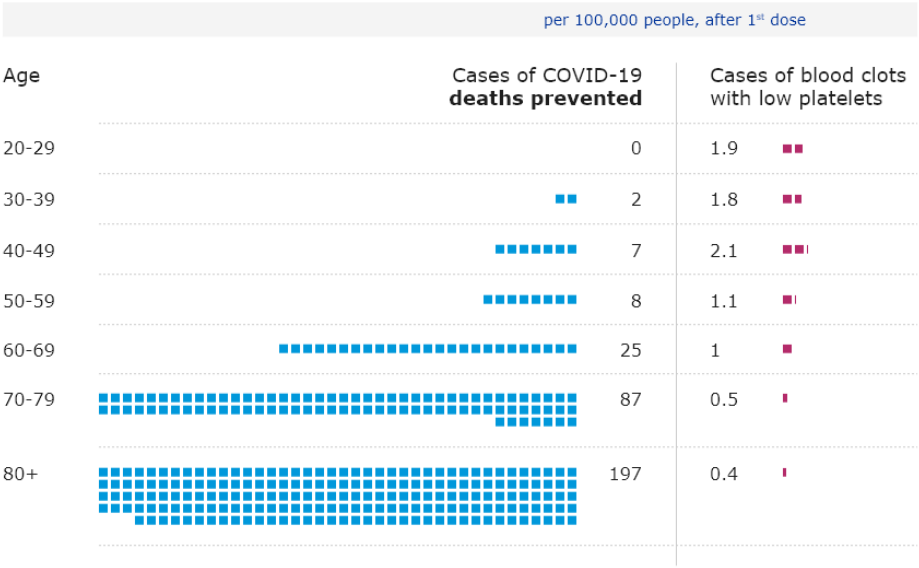
3. **COVID-19 deaths prevented with Vaxzevria compared with unusual blood clots with low platelets**

High infection rate*



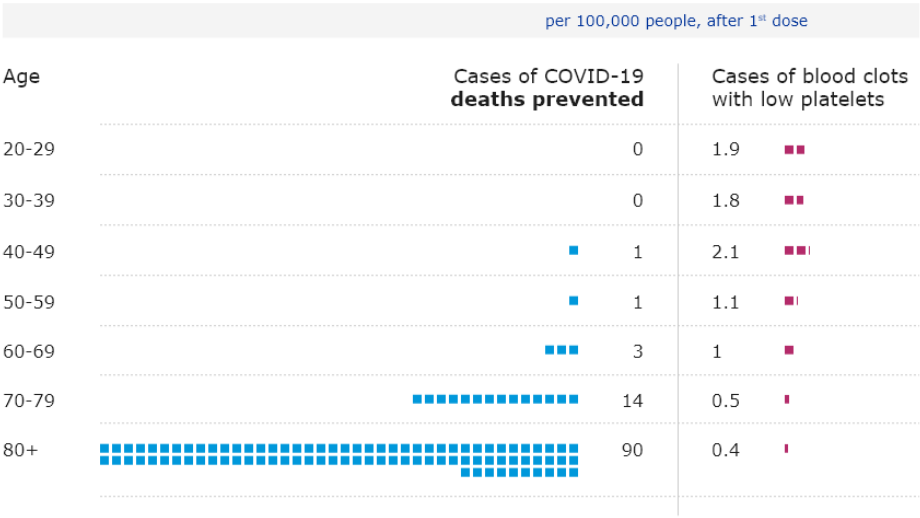
* "High" exposure: using virus circulation for January 2021 (incidence 886/100,000 population)

Medium infection rate*



* "Medium" exposure: using virus circulation for March 2021 (incidence 401/100,000 population)

Low infection rate*



* "Low" exposure: using virus circulation for September 2020 (incidence: 55/100,000 population)

Appendix 4

SAMPLE OF EVIDENCE: EXTENDED INTERVAL BETWEEN MRNA COVID-19 VACCINE DOSES

Sample references	Study	Results	Conclusion
Bernal et al Early effectiveness of COVID-19 vaccination with BNT162b2 mRNA vaccine and ChAdOx1 adenovirus vector vaccine on symptomatic disease, hospitalisations and mortality in older adults in England Preprint March 2021 https://khub.net/documents/135939561/430986542/Early+effectiveness+of+COVID+vaccines.pdf/ffd7161c-b255-8e88-c2dc-88979fc2cc1b?t=1614617945615	Case control study (UK) All adults in England ≥ 70 years and (over 7.5 million). All COVID-19 testing in the community among eligible individuals who reported symptoms between 8th December 2020 and 19th February 2021 Endpoints: Symptomatic PCR confirmed SARS-CoV-2 infection, hospitalisations and deaths.	Vaccine effectiveness v. symptomatic disease Pfizer MRNA: - those aged ≥80 yrs 28-34 days after dose 1: 70% 14 days after dose 2: 89% - those aged ≥70 yrs 28-34 days after dose 1: 61% ChAdOx1 - those aged ≥70 yrs 28 -34 days after dose 1: 60% >35 days after dose 1: 73% Further↓ risk of emergency hospitalisation/death post one dose: BNT162b: 43% & 51% (95%CI 37- ChAdOx1: 37 %	A single dose of either vaccine is approximately 80% effective at preventing hospitalisation and a single dose of BNT162b2 is 85% effective at preventing death with COVID-19 *Comment: Single dose of either vaccine effective in the short term even up to 35 days.* *Additional benefit from dose 2 Pfizer.*

Dagan et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting Published Feb 2021 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7944975/	Marched cohort observational study (Israel) Endpoint: SARS-CoV-2 infection, symptomatic disease, hospitalization, severe illness, and death following Pfizer COVID-19 vaccination. 14-20 days post 1st vaccine versus up to 7 days post second vaccine	Vaccine effectiveness days 14 - 20 post dose 1 & ≥7 days post dose 2: Documented infection: 46% & 92% Symptomatic Covid-19: 92% & 94% Hospitalization: 74% & 87% Severe disease: 62% & 92% Death from Covid-19: 72% & NA.	BNT162b2 effective v wide range of outcomes with effect from day 14 *Comment: Single dose very effective in the short term. No data on protracted interval*
Hall et al Effectiveness of BNT162b2 mRNA Vaccine Against Infection and COVID-19 Vaccine Coverage in Healthcare Workers in England, Multicentre Prospective Cohort Study (the SIREN Study) Published April 23, 2021 DOI:https://doi.org/10.1016/S0140-6736(21)00790-X	Cohort study (UK) Healthcare workers Effectiveness of vaccine 21 days post 1st dose and 7 days post 2nd dose	A single dose of BNT162b2 vaccine demonstrated vaccine effectiveness of 72% 21 days after first dose and 86% seven days after two doses in the antibody negative cohort.	First dose of BNT162b2 effective in working age adults against symptomatic and asymptomatic infection and at a time when B1.1.7 was circulating *Comment: Excellent effectiveness in the short term with additional benefit from dose 2.*
Hill et al Comparison between one and two dose SARS-CoV-2 vaccine prioritisation for a fixed number of vaccine doses Preprint March 2021	Modelling study (UK) Maximising averted deaths	We optimised outcomes for two different estimates of population size and relative risk of mortality for at-risk groups within the Phase 1 vaccine priority order in England, for different amounts of available vaccine and for different vaccine efficacies.	Vaccines offering relatively high protection from the first dose (compared to the efficacy derived from two doses) favour strategies that prioritise giving more people one dose rather than a smaller number two. The optimal mix of one and two doses between the

doi: https://doi.org/10.1101/2021.03.15.21253542			defined priority groups of Phase 1 shows a pattern of returning to give second doses to the highest risk groups as the number of available doses increases.
Romero-Brufau et al The Public Health Impact of Delaying a Second Dose of the BNT162b2 or mRNA-1273 COVID-19 Vaccine Preprint February 2021 doi: https://doi.org/10.1101/2021.02.23.21252299	Modelling Study (USA) Investigated agent-based modelling (ABM) to measure the relative impact of delaying second dose vaccine policies on infections, hospitalizations and mortality compared to the current on-schedule two dose regimen Did not state specific duration of delayed second dose	Total mortality per 100,000 for standard versus delayed second dose is 226 vs 179; 233 vs 207; and 235 vs 236; for 90%, 80% and 70% first-dose efficacy, respectively. These results suggest that higher first-dose efficacy estimates favour delaying the second dose, and that for a first-dose efficacy of 70%, there seems to be no meaningful difference between the standard and delayed-second-dose strategy	The results suggest under specific conditions, a decrease in cumulative mortality, infections, and hospitalizations can be achieved when the second vaccine dose is delayed. The benefits were observed when first dose vaccine > 70% and vaccination rates < 1% of the population per day *Comment: Optimised vaccine schedule will depend on levels of virus, vaccine effectiveness, availability of vaccines, and vaccine uptake, and thus vary by setting*
Vasileiou et al Effectiveness of First Dose of COVID-19 Vaccines Against Hospital Admissions in Scotland: National Prospective Cohort Study of 5.4 Million People Preprint March 2021	Prospective cohort (Scotland, 5.9m) Early Pandemic Evaluation and Enhanced Surveillance of COVID-19 (EAVE II) database includes data on 5.4 million people in Scotland Hospitalisation associated with COVID-19	Vaccine Effectiveness vs. COVID-19 related hospitalisation at 28-34 days post-vaccination For All Dose 1 BNT162b2 ChAdOx1 + 1-7 days 38% 70% +14 -20d 60% 74% +21-27d 72% 84% +28-34d 85% 94%	Both BNT162b2 & ChAdOx1 Were very effective at preventing hospitalisation, including in the very elderly following a single dose of vaccine over 28 – 34 days *Comment: Reassuring data on effectiveness of Astrazeneca*

https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3789264		+35-41 68% n/A +42 64% For ≥ 80 yrs Results of combined vaccine effect for prevention of COVID-19 related hospitalisation were comparable when restricting the analysis to those aged ≥80 years 81 at 28-34 days post-vaccination).	*vaccine in the elderly. Some decline in reported efficacy of the Pfizer vaccine after 34 days might reflect the small numbers with follow up or support the need to dose 2.*

Acknowledgements

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- Health Products Regulatory Authority
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- HSE Social Inclusion
- National Coagulation Centre
- NIAC members
- NIAC SpR Research Panel
- RCPI Communications Department

Amendments

29.04.2021

Page 13: Replacement of section inadvertently deleted *Note re vaccine selection for immunocompromised persons*