ROYAL COLLEGE OF PHYSICIANS OF IRELAND

National Immunisation Advisory Committee

RECOMMENDATIONS REGARDING ADENOVIRAL VECTOR VACCINES

NIAC | 13 May 2021

About NIAC

NIAC membership 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 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. Recommendations may be updated when more information becomes available.

All the authorised COVID-19 vaccines provide considerable benefits. The assessment of benefit/risk of adenoviral vector COVID-19 vaccines (Vaxzevria® and COVID-19 Vaccine Janssen®) in those aged 18-49 years is more favourable when rates of COVID-19 disease are high or increasing.

Thrombosis thrombocytopenia Syndrome (TTS) is a very rare side effect of authorised adenoviral vector vaccines. There is uncertainty as to whether the risk of TTS is greater for one adenoviral vaccine compared with the other. While more evidence is being collated, similar recommendations have been made for the two adenoviral vector vaccines.

The benefit/risk ratio of the adenoviral vector vaccines is favourable in all ages and very clearly demonstrated in those aged 50 years and older. Most cases of TTS occurred in those aged 18-49 years. As the risks of TTS may be higher in younger adults, NIAC has previously recommended the use of mRNA vaccines for those aged under 50 years and consideration of the single dose COVID-19 vaccine Janssen® if a two-dose mRNA vaccine schedule is not feasible.

When COVID-19 rates are high or increasing and/or the availability of mRNA vaccines is limited, adenoviral vector vaccines may be recommended for those aged 18-49 years to provide early protection.

When COVID-19 rates are low or moderate, as currently in Ireland, healthy people aged 40-49 years may choose to avail of an earlier adenoviral vector vaccine provided they have made an informed decision. This decision should be based on their understanding of the risk of developing TTS compared with the consequences of COVID-19, the options of other effective public health measures and the benefits of a prompt vaccine. Should a person choose not to avail of earlier adenoviral vector vaccination, they should be offered mRNA vaccine with their age cohort as previously planned.

There is no evidence of a higher risk of TTS following a second dose of Vaxzevria® and to date, information suggests the risk is substantially decreased. All those who have received one dose of Vaxzevria® should receive their second dose 12 weeks later. The extended interval of 16 weeks is permissible, if already scheduled.

NIAC recommends that all individuals should continue to practice recommended public health measures for prevention and control of COVIID-19 infection and transmission after COVID-19 vaccination.

Recommendations for adenoviral vector vaccines 13.05.2021

No change to the following recommendations

- All individuals should continue to practice recommended public health measures for prevention and control of COVID-19 infection and transmission after COVID-19 vaccination
- For all those aged **50 years and older**, any authorised COVID-19 vaccine is recommended
- mRNA vaccines are preferred for those **aged 16 years and older** who are immunocompromised
- For those **aged 16 to 49 years** mRNA vaccines are recommended
- For those **aged 18 to 49 years** the single dose COVID-19 vaccine Janssen® can be considered if a two-dose mRNA vaccination schedule is not feasible

Update to recommendations

1. Use of adenoviral vector COVID-19 vaccines in those aged 18 to 49 years

Healthy people **aged 40-49 years** may choose to avail of an earlier adenoviral vector vaccine, provided they have made an informed decision. This decision should be based on their understanding of the risk of developing TTS compared with the consequences of COVID-19 infection, the options of other effective public health measures and the benefits of a sooner vaccine.

Should a person choose not to avail of earlier adenoviral vector vaccination they should be offered mRNA vaccine with their age cohort as previously planned.

2. Contraindications to and appropriate use of adenoviral vector vaccines for those aged 18 to 49 years

A. Contraindications

There is no change to the contraindications to COVID-19 adenoviral vector vaccines for those aged 18 years and older (see Chapter 5a COVID-19)

B. Appropriate use

- If a two-dose mRNA vaccination schedule is not feasible, the single dose COVID-19 vaccine Janssen® can be considered (as previously recommended)
- When COVID-19 rates are high or increasing and/or the availability of mRNA vaccines is limited, adenoviral vector vaccines may be recommended for those **aged 18-49 years** to provide early protection.
- Healthy people **aged 40-49 years** may choose to avail of an earlier adenoviral vector vaccine, provided they have made an informed decision. This decision should be based on their understanding of the risk of developing TTS compared with the consequences of COVID-19 infection, the options of other effective public health measures and the benefits of a sooner vaccine.
- If an individual chooses not to avail of earlier vaccination with an adenoviral vector vaccine, they should be offered mRNA vaccine with their age cohort as previously planned.

3. The optimal approach and dosing schedule in those who have already received their first dose of Vaxzevria®

The interval between doses for those who had received a first dose was extended to 16 weeks pending information on the TTS risk after a second dose. There is no evidence of a higher risk of TTS following dose 2. Information to date suggests the risk is substantially decreased.

- Those who have received one dose of Vaxzevria® should receive their second dose 12 weeks later
    - The extended interval of 16 weeks is permissible if already scheduled
    - A shorter interval of 4 - <12 weeks may be used if circumstances warrant (e.g., pregnancy, imminent immunotherapy)

DOH request for advice

On 6 May 2021, NIAC received a request from the Department of Health (DOH) for advice on the following:

1. The relevant considerations, including safety and clinical, which should inform any potential offering of either of the adenoviral vector vaccines to individuals under 50 years of age
2. Whether there are other categories or age cohorts of individuals under 50 years of age for whom adenoviral vector vaccines may be contra-indicated or inappropriate
3. The optimal approach and dosing schedule in those who have already received their first dose of Vaxzevria®.

In forming any recommendations/advice, NIAC weighs the potential risks of any vaccine-associated harm against disease related risks, both to the individual and the community. We also consider other disease mitigation strategies including availability of other vaccines. NIAC's overall priority for the vaccination programme continues to be prevention of severe disease and death in the most vulnerable, and reduction of barriers that might prevent individuals being vaccinated.

NIAC reviewed available evidence and international practices, and engaged with the HPRA, HIQA, DOH, and other stakeholders.

NIAC has further considered the use of the authorised adenoviral COVID-19 vaccines with regard to their likely causal association with Thrombosis Thrombocytopenia Syndrome (TTS), its reported incidence, and a benefit /risk assessment in the Irish context. NIAC took into account the longer shelf life of both vaccines at normal refrigeration temperatures compared to mRNA vaccines and, in the case of COVID-19 Vaccine Janssen®, its authorisation as a single dose vaccine.

1. The relevant considerations, including safety and clinical, which should inform any potential offering of either of the adenoviral vector vaccines to individuals under 50 years of age

THROMBOSIS THROMBOCYTOPENIA SYNDROME

Thrombosis Thrombocytopenia Syndrome (TTS) (rare, unusual blood clots with low platelets) is a very rare side effect of Vaxzevria® and COVID-19 Vaccine Janssen®. Patients may present with either thrombosis, thrombocytopenia or both.

It is uncertain whether the risk of TTS is similar for both adenoviral vector vaccines. There is also uncertainty as to the incidence of TTS in all populations, with estimates ranging from 1/40,000 to 1/million depending on time of reporting and population studied. Increased awareness of the condition has likely resulted in an increase in the reporting rates of TTS.

TTS has been reported after both vaccines but there is insufficient evidence to determine if the rate differs significantly between the two vaccines.

To date, no predisposing risk factors have been identified, although the majority of cases have been reported in females under the age of 60, with a decrease in case reports with increasing age. There is insufficient evidence to perform a gender stratified analysis.

The overall case fatality rate may decrease as the clinical spectrum of TTS is broadened incorporating those with a milder disease and an increase in awareness with early recognition allows prompt diagnosis and management.

TTS FOLLOWING VAXZEVRIA®

The European Medicines Agency (EMA) has recently estimated TTS to occur in 1/100,000 people vaccinated with Vaxzevria®, following a TTS specific case search of the Eudravigilance data with 142 cases reported and an estimated exposure of 18 million doses as of 13 April 2021.

An EMA assessment report of Vaxzevria® from 26 April 2021 showed that the benefits of vaccination increase with increasing age and increasing infection rates. Conversely, the rates of TTS in those aged under 50 years were two to four times greater than the rates in those 50 years and older (Table 1). A case reporting rate by gender was not provided, as exposure data was not available.

Table 1. Age stratified TTS cases for Vaxzevria® after dose 1, EU/EEA

Age in years	Total vaccinated (millions)	TTS /100,000	TTS/100,000*	Deaths/100,000*
20-29	1.3	1.9	2.7	0.1
30-39	1.9	1.8	2.1	0.5
40-49	2.8	2.1	2.7	0.9
50-59	3.3	1.1	1.4	0.2
60-69	5.1	1.0	1.3	0.3
70-79	3.1	0.5	0.9	0.2
80+	0.8	0.4	0.4	0.2

Source: HPRA

*Sensitivity analysis for underreporting (0% first 7 days; 20 between day 7-20; 50% after day 20

**Outcome not reported in all cases)

A study from Norway and Denmark of 281,264 persons aged 18 – 65 years (median age 45 years, 80% female) reported 11 excess venous thromboembolic events per 100,000 vaccinations, including an excess of CVST events of 2.5/100,000, i.e., 1/40,000 vaccinations.

UK data on 28 April 2021 (Table 2) showed the reported rate of TTS was higher in younger adult age groups. The rate was higher in females compared to males, although this was not seen across all age groups and the difference was small. Five of the cases were reported from Northern Ireland.

In Ireland, following the initial reports of TTS, there was a temporary pause in the administration of Vaxzevria®. This enabled collation and dissemination of information regarding its recognition and management prior to resumption of the vaccination programme. To date, there have been a small number of cases (less than 5) notified to the HPRA from approximately 500,000 doses administered. The individuals concerned are reported as discharged from hospital.

TTS FOLLOWING COVID-19 VACCINE JANSSEN®

Reports of TTS following vaccination with COVID-19 Vaccine Janssen® are only available from the US. As of 12 May, TTS associated with COVID-19 Vaccine Janssen® has not been reported in the EEA, with limited use of the vaccine.

Current US estimates of 12 May 2021 suggest that TTS occurs at an overall rate of 1/312,000 vaccinations (28 cases after almost 9 million doses) and that there may be a greater risk for women aged 50 years and under. Based on this, the risk for women <50 years may be 1/110,000 (Table 2).

As seen in the US above, in the UK, TTS cases after Vaxzevria® respectively were initially reported predominantly in females. However, in the UK, this has not been seen across all age groups and the sex differences are now small.

Table 2. Chronology of TTS case reporting by vaccine, UK and US

	Vaxzevria®			Janssen®		
Source	**MHRA**			**CDC**		
Date	5/4/21	21/4/2021	28/4/2021	12/4/2021	21/4/2021	7/05/2021
Estimated vaccine doses (millions)	21.6	26.4	28.5	6.86	7.98	8.73
Cases	100	209	242	6	17	28
Male: Female	39:61	120:89	100:141	1*:6	1*:16	6:22
Age (years)	18 – 85	18 – 93	18 – 93 70% < 60	18 - 48	18 – 60 82% <50	18-59 82% <50
TTS reporting rate	1/216,000	1/126,000	1/116,000	<1/1,000,000	1/500,000 1/266,000**	1/312,000 1/110.000**
Dose 1 **Dose 2**		1/100,000 1/1,000,000	1/95,000 1/1,000,000	n/a	n/a	n/a
TTS death rate		1/600,000	1/500,000		1/ 2,600,000	1/3,000,000

Abbreviations used in the table
Medicines and Healthcare products Regulatory Agency, UK
Centers for Disease Control and Prevention, USA

*1 case TTS in a young male in the phase 3 trial

** Rate in women aged <50 years

EFFICACY AND EFFECTIVENESS OF VAXZEVRIA® AND COVID-19 VACCINE JANSSEN®

All authorised COVID-19 vaccines have high efficacy against severe disease and almost 100% protection against death.

There is limited evidence of protection against asymptomatic infection and transmission of SARS-CoV-2 by both adenoviral vector and mRNA vaccines. Efficacy against symptomatic infection varies from 63% and 66% for Vaxzevria® and COVID-19 Vaccine Janssen® and up to 95% for the mRNA vaccines. However, efficacy rates are not comparable as clinical trials were carried out at different times, in different countries, with different disease prevalence and different circulating strains.

Vaxzevria® has proved effective when used in areas where the B1.1.7 variant was circulating, although efficacy against the B.1.351 variant was poor. COVID-19 vaccine Janssen® had an efficacy of 67% in clinical trials where the B.1.335 and P.2 variants were circulating.

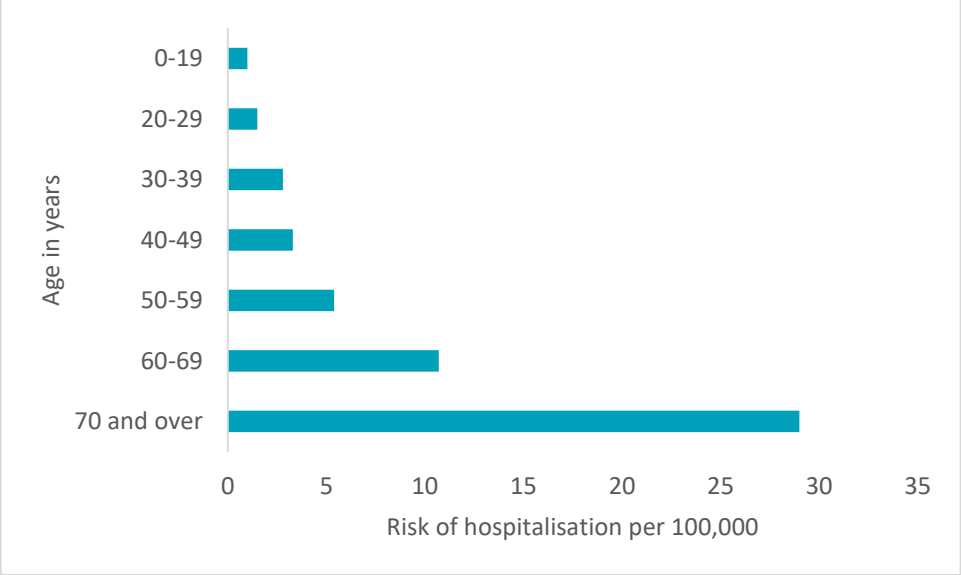
ADENOVIRAL VECTOR VACCINES IN COVID-19 VACCINATION PROGRAMMES

The WHO European Technical Advisory Group of Experts on Immunization (ETAGE) noted that benefit–risk assessments of vaccines may differ from country to country. ETAGE recommended that countries should consider their epidemiological situation, individual and population-level risks, availability of other vaccines, and alternate options for risk mitigation when considering the place of adenoviral vector vaccines in their COVID-19 immunisation programmes.

In Ireland the weekly incidence rate of COVID-19 infections in March and April 2021 was 67/100,000. The incidence ranged from 95/100,000 in those aged 20-29 years to 66/100,000 in those aged 40-49 years.

The risk of hospitalisation decreases progressively down the age cohorts (Figure 1)

Figure 1. Hospitalisation risk ratio for COVID-19, March-April 2021 - Ireland



Source: Health Protection Surveillance Centre Computerised Infectious Disease Reporting extract 06.05.2021 Cases notified to Midnight 05.05.2021

The UK based Winton Centre for Risk Evaluation and evidence Communication contextualised the benefits and risks of TTS and COVID-19 based on UK data (see appendix 1). They defined very low exposure risk as a weekly incidence of 42/100,000 and low exposure risk as 140/100,000. Current epidemiology places Ireland in the very low to low-risk exposure category.

The estimates of benefit were based on a fixed vaccine efficacy of 80% against ICU admission, over a four-month period. The benefits underrepresent the overall vaccine benefit. They do not consider benefit of hospitalisations averted and reduced transmission, or risk of 'long COVID'. The benefits continue over the lifetime of the vaccine's protection. The risks from vaccination occur only at the time after vaccination. Thus, over time, the benefits will increase but the risks will not.

The TTS estimates were based on spontaneous reports and have uncertainty around them, because of the small number of reports, and cases may not have been reported.

The EMA reported similar findings of the benefit/risk of Vaxzevria® compared to TTS in the EEA.

Consideration of these factors underpinned the NIAC advice of 26 April 2021. The benefit/risk ratio of the adenoviral vector 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.

A benefit/risk ratio assessment by the Canadian National Advisory Committee on Immunisation of 3 May 2021, demonstrated the progressive age-related benefit of vaccination by 10-year cohorts across all levels of disease activity. As rates of TTS increase from 1/500,000 to 1/100,000 and as disease activity levels decreases, the expected incidence of TTS approaches and at times exceeds the numbers of potentially prevented ICU admissions and deaths.

Thus, the adenoviral vector vaccines have considerable benefits, not all of which are accounted for in these risk/benefit assessments, such as the prevention of infection and of consequences such as long COVID. The benefits in preventing severe disease increase with increasing age and are clearly evident for those aged 50 and older. There is a risk of a very rare but serious condition, TTS, with its significant associated mortality that appears higher in the younger age groups. The benefits and risks are more finely balanced as age decreases and as the exposure risk in the community also falls.

INTERNATIONAL PRACTICE

The complexity of the situation in different countries, in different stages of disease epidemiology and vaccine roll-out is reflected in the diversity of approach, ranging from exclusion of both adenoviral vector vaccines to no age restrictions for either vaccine.

Request 2: Whether there are other categories or age cohorts of individuals under 50 years of age for whom adenoviral vector vaccines may be contraindicated or inappropriate

CONTRAINDICATIONS

The only contraindications to adenoviral vector COVID-19 vaccines are:

- Anaphylaxis (serious systemic allergic reaction requiring medical intervention) following a previous dose of the vaccine or any of its constituents (including polysorbate 80)
- A second dose of Vaxzevria® should not be given to anyone who developed TTS after the first dose
- COVID-19 Vaccine Janssen® should not be given to anyone who developed TTS after Vaxzevria®

If contraindications to the use of an adenoviral vector vaccine exist, a mRNA vaccine is recommended across all ages.

SPECIAL CONSIDERATIONS RE APPROPRIATE USE OF ADENOVIRAL VECTOR VACCINES

NIAC assesses how best to use authorised COVID-19 vaccines to achieve the greatest public health benefits. This assessment is based on the epidemiology of COVID-19 disease and risks by age group or medical condition, vaccine safety and effectiveness and ethical principles.

mRNA vaccines are recommended for those age 16-49 years, including for those with medical conditions with very high or high risk of severe COVID-19 disease. If a two-dose mRNA vaccination schedule is not feasible, the single dose COVID-19 vaccine Janssen® can be considered for those aged 18-49 years. (Only Comirnaty® is authorised for those aged 16 years and older.)

NIAC recognises that all the authorised vaccines afford considerable benefits. The assessment of benefit/risk of adenoviral vector COVID-19 vaccines in those aged 18-49 years is more favourable when rates of COVID-19 disease are high or increasing.

Even when disease rates are low or moderate, the benefits of an mRNA vaccine may be significantly eroded if there is undue delay and alternative vaccines are available. Individuals aged 40-49 years could be given an opportunity to choose an earlier adenoviral vector vaccine provided the person has made an informed decision. This decision should be based on their understanding of the risk of developing TTS compared with the consequences of COVID-19 infection, the options of other effective public health measures and the benefits of an early adenoviral vector vaccine.

If an individual chooses not to avail of earlier vaccination with an adenoviral vector vaccine, they should be offered an mRNA vaccine with their age cohort as previously planned.

Request 3: The optimal approach and dosing schedule in those who have already received their first 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 an 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.

In the UK, of 242 TTS reported cases to 28 April 2021, only six occurred after the second dose. To date, over 6 million second doses have been given. Very preliminary available evidence suggests that the risk of TTS may not be higher and is possibly substantially lower (1 case per million) after a second dose.

INTERNATIONAL RECOMMENDATIONS

World Health Organization (WHO)

In line with the updated interim SAGE (the Strategic Advisory Group of Experts) recommendations, ETAGE (European Technical Advisory Group of Experts on Immunization) acknowledges that the two-dose schedule and the interval between the doses of Vaxzevria® vaccines remain unchanged.
Ad-hoc meeting of ETAGE, 28 April 2021

European Medicines Agency (EMA)

"There has not been enough exposure and follow-up time to determine whether the risk of blood clots with low blood platelets after a second dose will differ from the risk after the first dose. At present there are no or limited data to change current recommendations."
AstraZeneca's COVID-19 vaccine: benefits and risks in context, 23 April 2021

Joint Committee on Vaccines and Immunisation (JCVI) on AstraZeneca (AZD1222) (Vaxzevria ®)

"JCVI considers that there continues to be no safety concerns for this extremely rare adverse event following receipt of a second dose of AstraZeneca (AZD1222) vaccine. All those who have received a first dose of the AstraZeneca (AZD1222) vaccine should continue to be offered a second dose of AstraZeneca (AZD1222) vaccine, irrespective of age. The second dose will be important for longer lasting protection against COVID-19."
Use of the AstraZeneca COVID-19 (AZD1222) vaccine: updated JCVI statement, 7 May 2021

Based on the above, NIAC concluded that there is insufficient evidence to recommend a change from the authorised two-dose Vaxzevria® schedule and no evidence to date to support giving a mRNA vaccine instead of a second dose of Vaxzevria®.

There is no evidence of an increased risk of TTS after the second dose of Vaxzevria® which is essential to enhance the durability of protection. The second dose should be given to all vaccine recipients at an interval of 12 weeks and up to 16 weeks is permissible if already scheduled. A shorter interval of 4 - <12 weeks may be used if circumstances warrant.

Recommendations for adenoviral vector vaccines 13.05.2021

No change to the following recommendations

- All individuals should continue to practice recommended public health measures for prevention and control of COVID-19 infection and transmission after COVID-19 vaccination
- For all those aged **50 years and older**, any authorised COVID-19 vaccine is recommended
- mRNA vaccines are preferred for those **aged 16 years and older** who are immunocompromised
- For those aged **16 to 49 years** mRNA vaccines are recommended
- For those aged **18 to 49 years** the single dose COVID-19 vaccine Janssen® can be considered if a two-dose mRNA vaccination schedule is not feasible

Update to recommendations

1. Use of adenoviral vector COVID-19 vaccines in those aged 18 to 49 years

Healthy people **aged 40-49 years** may choose to avail of an earlier adenoviral vector vaccine, provided they have made an informed decision. This decision should be based on their understanding of the risk of developing TTS compared with the consequences of COVID-19 infection, the options of other effective public health measures and the benefits of a sooner vaccine.

Should a person choose not to avail of earlier adenoviral vector vaccination they should be offered mRNA vaccine with their age cohort as previously planned.

2. Contraindications to and appropriate use of adenoviral vector vaccines for those aged 18 to 49 years

A. Contraindications

There is no change to the contraindications to COVID-19 adenoviral vector vaccines for those aged 18 years and older (see Chapter 5a COVID-19)

B. Appropriate use

- If a two-dose mRNA vaccination schedule is not feasible, the single dose COVID-19 vaccine Janssen® can be considered (as previously recommended)
- When COVID-19 rates are high or increasing and/or the availability of mRNA vaccines is limited, adenoviral vector vaccines may be recommended for those **aged 18-49 years** to provide early protection.
- Healthy people **aged 40-49 years** may choose to avail of an earlier adenoviral vector vaccine, provided they have made an informed decision. This decision should be based on their understanding of the risk of developing TTS compared with the consequences of COVID-19 infection, the options of other effective public health measures and the benefits of a sooner vaccine.
- If an individual chooses not to avail of earlier vaccination with an adenoviral vector vaccine, they should be offered mRNA vaccine with their age cohort as previously planned.

3. The optimal approach and dosing schedule in those who have already received their first dose of Vaxzevria®

The interval between doses for those who had received a first dose was extended to 16 weeks pending information on the TTS risk after a second dose. There is no evidence of a higher risk of TTS following dose 2. Information to date suggests the risk is substantially decreased.

- Those who have received one dose of Vaxzevria® should receive their second dose 12 weeks later
    - The extended interval of 16 weeks is permissible if already scheduled
    - A shorter interval of 4 - <12 weeks may be used if circumstances warrant (e.g., pregnancy, imminent immunotherapy)

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Appendix

Winton Centre for Risk Evaluation and evidence Communication Latest data from the MHRA on blood clots associated with the Astra Zeneca COVID-19 vaccine 6 May 2021

Figure 1. Vaxzevria® benefits calculated with an incidence level of 'very low exposure' 0.6 (roughly the current - as of 30th April - incidence level of COVID-19 in the UK)

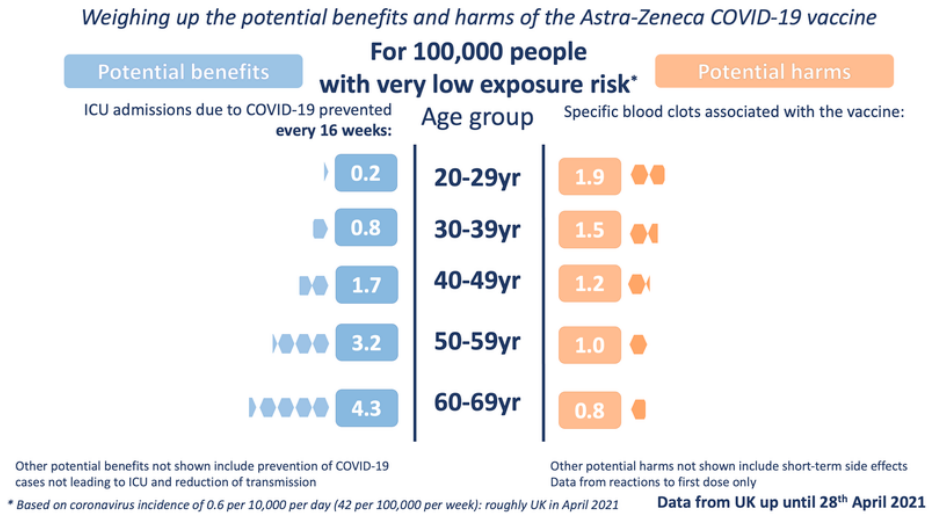
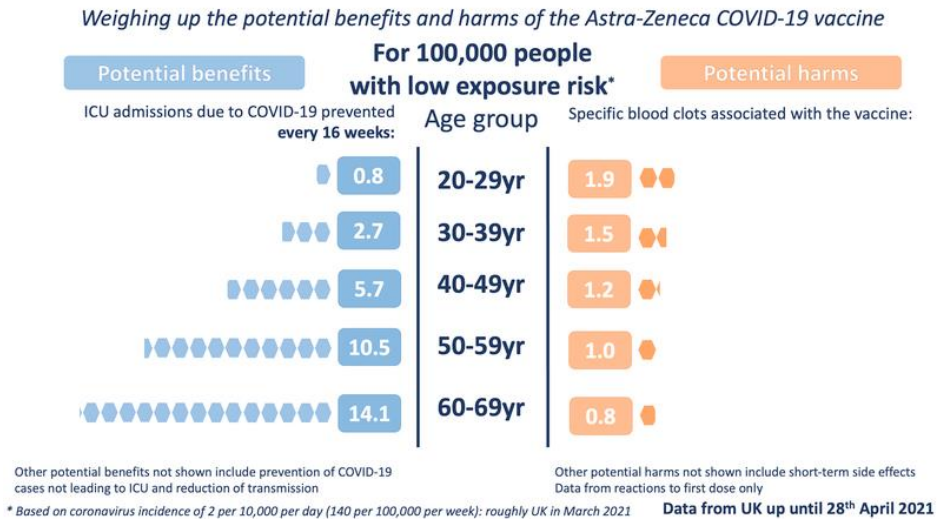


Figure 2. Vaxzevria® benefits calculated with an incidence level of 'low exposure' (incidence of 2 in 10,000 per day - roughly the UK in March 2021)



Amendments

13.05.2021 12.30

Page 2 recommendations box: final sub bullets listed separately for clarity