

Overview of EU/EEA country recommendations on COVID-19 vaccination with Vaxzevria, and a scoping review of evidence to guide decision-making

18 May 2021

Key messages

In March 2021, following the notification of cases of blood clots with low blood platelets in people who had received Vaxzevria (AZD1222) (previously COVID-19 Vaccine AstraZeneca), the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) initiated a detailed review of safety data on cases of thromboembolic events received through the EUDRAVIGILANCE database. On 16 April 2021, EMA PRAC concluded that thromboembolic events associated with thrombocytopenia (known as 'Thrombosis with Thrombocytopenia Syndrome' - TTS) are a very rare side effect of Vaxzevria and the product information sheet was updated accordingly. Based on a review of data on vaccination and disease epidemiology, EMA's Committee for Medicinal Products for Human Use (CHMP) concluded that the overall benefits of Vaxzevria outweigh risks from adverse events, including TTS. However, the benefit of vaccination with Vaxzevria - in terms of averted hospitalisations, ICU admissions and deaths - rises as age and infection rates increase. EMA recommendations in terms of a second dose of Vaxzevria remain in line with the product information (i.e. 4–12 weeks interval).

As a result of the safety signal and subsequent evaluation, several EU/EEA countries have changed their recommendations on use of Vaxzevria. Based on information collected in a survey sent by ECDC to the EU/EEA National Immunisation Technical Advisory Groups (NITAGs), a follow-up webinar and a desk review of official sources, as of 12 May 2021, EU/EEA countries had changed their recommendations on use of Vaxzevria as follows:

- In all, 15 EU/EEA countries have adopted specific recommendations to administer Vaxzevria only to certain age groups, in most cases the elderly above a certain age.
- A total of 12 countries recommend use of Vaxzevria based on the current EMA summary of product characteristics (with certain exceptions linked to history or risk of thromboembolic events and pregnant women).
- Two countries have discontinued its use.

In addition, twenty EU/EEA countries currently recommend the administration of Vaxzevria as a second dose in individuals already having received a first dose of Vaxzevria. This includes seven countries with revised recommendations in terms of age restriction, but where the second dose of Vaxzevria is recommended to all individuals who received the first one, irrespective of age. Five countries have revised their recommendations and will administer the second dose with an mRNA vaccine (Comirnaty by BioNTech/Pfizer or COVID-19 Vaccine Moderna).

Options to complete a vaccination course following the administration of a first dose of Vaxzevria include:

- Vaxzevria as a second dose to everyone who received the first dose;
- mRNA COVID-19 vaccine as a second dose;
- another adenovirus vector vaccine as a second dose;
- no second dose or delayed interval between first and second dose.

A review of the evidence available to inform decisions on these options indicates that the empirical data currently available to guide a change in recommendations are limited. TTS remains a serious but very rare side effect of Vaxzevria, against which the public health impact of delayed vaccination programmes due to changed recommendations for Vaxzevria usage need to be assessed. This risk-benefit analysis will differ for countries and individuals, and should take into account the local epidemiological situation and availability of other authorised COVID-19 vaccines.

Suggested citation: European Centre for Disease Prevention and Control. Overview of EU/EEA country recommendations on COVID-19 vaccination with Vaxzevria, and a scoping review of evidence to guide decision-making. 18 May 2021. Stockholm: ECDC; 2021.

Stockholm, May 2021

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Scope of this document

This technical report provides information on the following:

- An overview of the regulatory procedures undertaken by the European Medicines Agency in response to the safety signal of rare blood clots associated with low platelet count after administration of Vaxzevria.
- An overview of the administration of Vaxzevria in EU/EEA countries, including current status of policies and recommendations on its use.
- Options for completing the vaccination course in individuals who received a first dose of Vaxzevria, based on current policies in EU/EEA countries and available scientific evidence.

This technical report provides a summary of the evidence available at the time of the publication and what will be required in the future to support EU/EEA countries taking decisions on administration of the second dose, following a first dose of Vaxzevria. Since new evidence is being generated continuously and safety monitored on an ongoing basis, it is essential for readers to consider the latest available information.

Target audience

Target audiences for this document are the European Commission, the Health Security Committee (HSC), the EU/EEA National Immunisation Technical Advisory Groups (NITAGs), national public health institutes and ministries of health in the EU/EEA, and public health experts and decision-makers at national and subnational level.

Background

Vaccine roll-out in the EU/EEA

The roll-out of COVID-19 vaccine campaigns is progressing in the EU/EEA, with phased prioritisation of certain population groups and the gradual expansion of access as vaccine uptake and availability of supplies increase. Countries have prioritised healthcare workers, residents and personnel in long-term care facilities and the elderly (with various lower age thresholds), and are gradually progressing to younger age groups, social care personnel, and people with certain comorbidities. As the vaccine deployment progresses, countries are facing challenges related to the supply and timing of delivery of COVID-19 vaccines. Among the most common are logistics for storage, transport and administration; wastage of doses; shortages in staffing and equipment and communication challenges relating to misinformation concerning COVID-19 vaccines [1,2].

As of week 17 (2 May 2021), the cumulative vaccine uptake in EU/EEA countries is steadily increasing, with median uptake of the first dose at 30% (range: 10.6–50.5%) and 11.6% (range: 2.5–25.8%) for the full vaccination course (data from all 30 EU/EEA countries). The median cumulative uptake is higher in persons aged 80 years and above, reaching 78% (range: 10.1–100%) for the first dose and 56.1% (range: 2.4–97.8%) for the full vaccination (24 EU/EEA countries reporting). In healthcare workers, the median cumulative uptake of the first dose reached 80.2% (range: 20.4–100%) and 53.7% (range: 17.2–100%) for the full vaccination course (16 countries reporting) [3].

Currently, four COVID-19 vaccines have received conditional marketing authorisation in the EU following evaluation by EMA: Comirnaty by BioNTech/Pfizer (BNT162b2); COVID-19 Vaccine Moderna (mRNA-1273); Vaxzevria, previously COVID-19 Vaccine AstraZeneca (AZD1222) and COVID-19 Vaccine Janssen (Ad26.COV 2.5) [4]. Following a recommendation from EMA, Vaxzevria received conditional market authorisation from the European Commission on 29 January 2021 for use in people from 18 years of age to prevent COVID-2019 [5] and its administration began in EU/EEA countries during the first week of February 2021 (week 5, 2021) [2].

Vaxzevria and thrombosis with thrombocytopenia syndrome

Administration of Vaxzevria in EU/EEA countries started in February 2021. In March 2021, in light of thromboembolic events temporally linked to the administration of Vaxzevria, some Member States and EMA initiated a detailed review of safety data [6,7]. Most of these events occurred in people under 55 years of age and the majority were women, which might be influenced by the prioritisation in many countries to vaccinate healthcare workers with Vaxzevria. In parallel to this investigation, several (21) EU/EEA countries temporarily paused vaccination with Vaxzevria as a precautionary measure.

On 18 March 2021, based on a preliminary assessment of cases, EMA concluded that, despite possible links, the benefits of Vaxzevria in preventing COVID-19 and its associated risk of hospitalisation and death, outweigh the risks of side effects. Many countries that had temporarily suspended Vaxzevria therefore resumed its use. The favourable risk-benefit profile of Vaxzevria was confirmed after EMA's Pharmacovigilance Risk Assessment Committee (PRAC) and Committee for Medicinal Products for Human Use (CHMP) made several rounds of investigation into safety data [7,8]. The review did not identify any specific risk factors, such as age, gender or a previous medical history of clotting disorders. PRAC concluded that these thromboembolic events should be listed as very rare side effects of Vaxzevria [9] and on 16 April 2021, the product information sheet was updated accordingly [10].

Furthermore, EMA's CHMP undertook a review of data on vaccination and disease epidemiology (e.g. infection rates, hospitalisations, morbidity and mortality due to COVID-19) to put the risks of Vaxzevria into context against the benefits of ongoing vaccination campaigns. CHMP concluded that the benefits of vaccination in terms of averted hospitalisations, ICU admissions and deaths, rise as age and infection rates increase [11], although data were insufficient to assess benefits and risks with regard to sex. CHMP also recommended that a second dose of Vaxzevria should continue to be given in line with the product information (i.e. 4 to 12 weeks after the first dose) [12].

Since 9 April 2021, PRAC had been concurrently reviewing very rare cases of cerebral venous sinus thrombosis (CVST), in most cases associated with thrombocytopenia, that occurred in the United States following use of Janssen's COVID-19 vaccine [13-16]. On 20 April 2021, PRAC concluded that a link was possible and that a warning about unusual blood clots with low blood platelets should be added to the product information as very rare side effects of COVID-19 Vaccine Janssen. However, as for Vaxzevria, this side effect is very rare and the overall benefits of COVID-19 Vaccine Janssen in preventing COVID-19 outweigh the risks [13].

On 21 April 2021, the Brighton Collaboration published an interim case definition for these thromboembolic events associated with thrombocytopenia as 'Thrombosis with Thrombocytopenia Syndrome' (TTS). The purpose of the interim case definition is to standardise the identification of cases that should be investigated using a harmonised protocol [17,18]. In this document, we will refer to all thromboembolic events associated with thrombocytopenia as TTS.

In a recent meeting, the European Technical Advisory Group of Experts on Immunization (ETAGE), a WHO expert group, concluded that the overall benefits of Vaxzevria in protecting against COVID-19 outweigh potential risks. ETAGE highlights the importance of evidence-based decision-making on the use of Vaxzevria, especially in relation to local data on disease epidemiology and other public health measures, as well as on hospitalisation and deaths due to COVID-19 per age group. They also emphasise the importance of estimating benefit-risk in the context of availability of other authorised COVID-19 vaccines [19].

Risk factors and the biological mechanism for TTS is still being investigated. No evidence of an increased risk, or any other risk factors have been found to date for those with clotting or platelet disorders. A recently published study summarises the clinical and laboratory features of 11 patients in Germany and Austria who developed TTS following Vaxzevria vaccination. Authors concluded that vaccination with ChAdOx1 nCov-19 (Vaxzevria) can result in the rare development of immune thrombotic thrombocytopenia, mediated by platelet-activating antibodies against PF4, which clinically mimics autoimmune heparin-induced thrombocytopenia. Findings may have clinical implications, in terms of awareness of adverse effects, assays for investigations of potential cases, and for treatment [20]. Additional studies from Norway and the UK have also found antibodies to PF4 in the majority of patients who developed TTS after vaccination with Vaxzevria [21,22].

Methods

The information presented in this technical report comes from the following sources:

- Data reported by EU/EEA countries to the European Surveillance System (TESSy) on the number of weekly doses of COVID-19 vaccines distributed by manufacturer to each country and administered, including vaccine product and age group.
- Information provided through an ECDC survey sent to EU/EEA NITAG collaboration members on current recommendations for the use of Vaxzevria, including the administration of a second COVID-19 vaccine dose in individuals previously vaccinated with Vaxzevria. This request was submitted on 12 April 2021 and responses were received until 19 April 2021 - see request for information in Annex 1.) In total, 23 NITAG collaboration members provided information.
- The request was followed by an EU/EEA NITAG collaboration webinar on 15 April 2021, where further information was shared among participants.
- Further information was gathered through a review of public sources (on 4 May 2021).
- Rapid review of scientific literature on the efficacy and effectiveness of a single dose of Vaxzevria (outcomes: infection, severe disease, hospitalisation, death); the safety of Vaxzevria in various groups; age-restriction (vaccine efficacy and effectiveness in different age groups, risk for event in different age groups); evidence of heterologous vaccination schedules; evidence of risk of TTS after a second dose Vaxzevria.
- The technical report was reviewed, and further inputs provided by EU/EEA NITAG collaboration Steering Committee members (reviewed by 3 May 2021) and by EMA (10 May 2021).

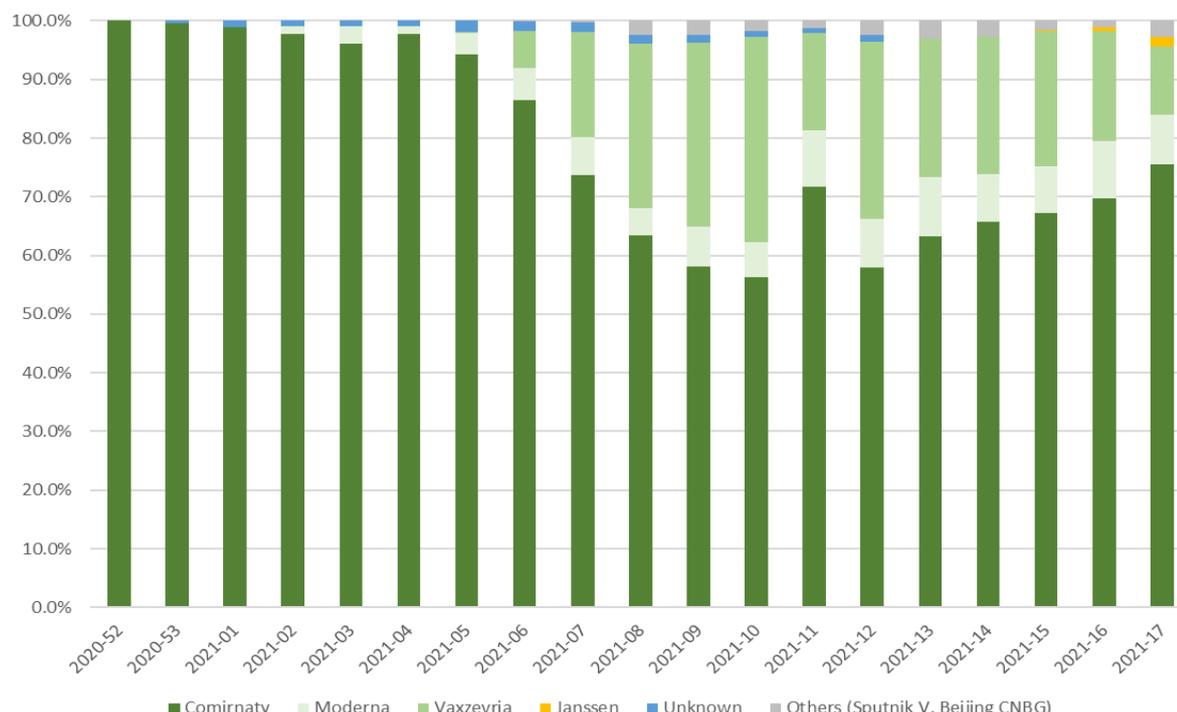
Results

Current supply and administration of Vaxzevria in the EU/EEA

As of week 17, 2021 (2 May 2021), a total of 43 651 763 doses of Vaxzevria have been distributed to EU/EEA countries, which represents 23.8% of the total number of COVID-19 vaccine doses distributed via the European Commission’s Vaccine Strategy.

At the same time, a total of 29 607 751 doses of Vaxzevria have been administered in the EU/EEA, almost all of them as first doses (97.9%) (data reported to TESSy by 30 countries). Vaxzevria accounts for 19.3% of the COVID-19 vaccine doses administered in EU/EEA countries since the beginning of the rollout (70.7% Comirnaty; 7.4% Moderna; 0.3% Janssen; 1.8% others; 0.5% unspecified vaccine products). Figure 1 shows the proportion of vaccine doses administered in EU/EEA countries by vaccine product by reporting week.

Figure 1. Proportion of COVID-19 vaccine doses administered in EU/EEA countries by vaccine product per week



Source: TESSy; data reported by 30 EU/EEA countries, as of 2 May 2021.

As of 2 May 2021, 66.3% of the total number of Vaxzevria doses distributed to EU/EEA countries had been administered (data from 29 EU/EEA countries; missing data on doses distributed to Malta). The trend in the proportion of Vaxzevria supplies used in the EU/EEA has been increasing overtime, with the exception of a reduction in week 13, probably due to the temporary pause in administration of Vaxzevria during the investigation by EMA’s PRAC in several countries, and more recently in week 17 (Figure 2).

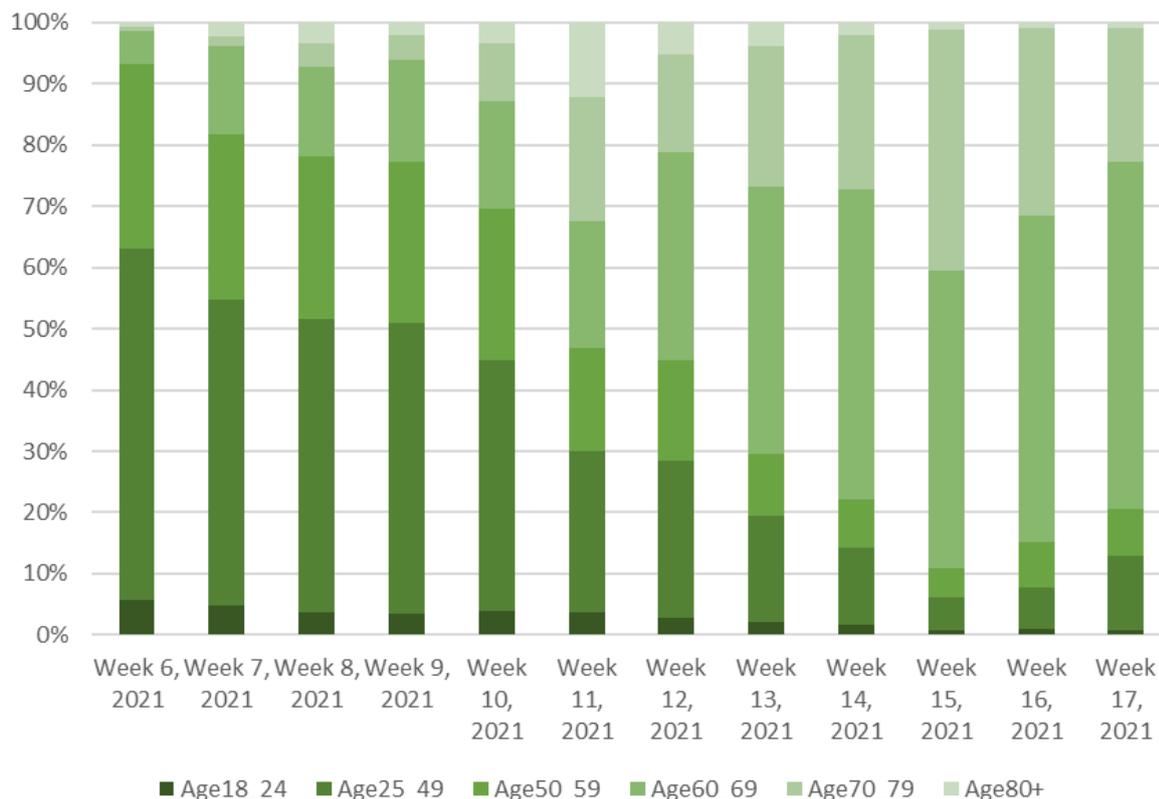
Figure 2. Cumulative doses of Vaxzevria distributed and administered and proportion used in EU/EEA countries per week



Source: TESSy; data reported by 29 countries, as of 2 May 2021 (missing complete data from Malta).

The administration of Vaxzevria doses by age group has significantly changed over time in EU/EEA countries, probably due to the progress in vaccine uptake in target groups and the update of national recommendations. During the first few weeks after the introduction of Vaxzevria into national vaccination programmes in early February, many countries prioritised its use in younger age groups. This was mainly due to the limited evidence available on efficacy in elderly people because of the low number of participants over the age of 55 included in the clinical trials. Given the subsequent accumulation of evidence on its effectiveness in the elderly [23-28], and the fact that TTS has mainly occurred in young adults, many countries adapted their vaccination policies and recommendations to prioritise use of Vaxzevria in older age groups (See Table 1 below). During week 17, 2021 (26 April to 2 May), 79.4% of doses of Vaxzevria were administered to people aged 60 years and above (Figure 3).

Figure 3. Proportion of Vaxzevria doses administered by age group in EU/EEA countries per week

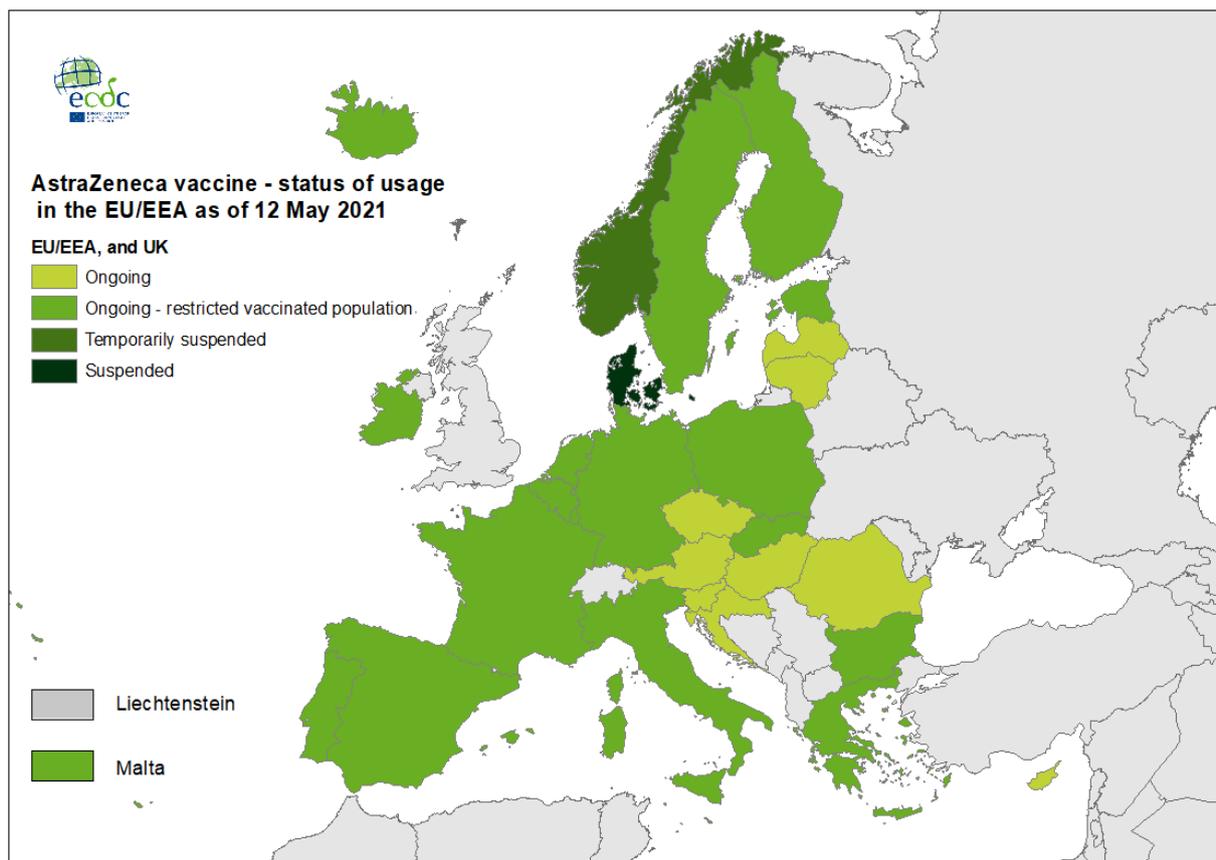


Source: TESSy; data reported by 24 EU/EEA countries as of 2 May 2021.

EU/EEA country recommendations on the use of Vaxzevria

This section provides an overview of the current status of recommendations on the use of Vaxzevria in EU/EEA countries. As of 12 May 2021, 27 EU/EEA countries were using Vaxzevria in their COVID-19 vaccination programmes, while two (Denmark and Norway) had discontinued its administration (Vaxzevria was never included in the COVID-19 vaccination programme in Liechtenstein).

During PRAC’s investigation into thromboembolic events in people who had received Vaxzevria and following the update of the product information listing these events as very rare side effects [29], EU/EEA countries have been revising and updating their policies and recommendations for the use of Vaxzevria (see Figure 1 and Table 1 for the current status based on available information).

Figure 4. Map showing status of Vaxzevria usage in EU/EEA countries, as of 12 May 2021

The boundaries and names shown on this map do not imply official endorsement by the European Union.

Date of production 12 May 2021

Source: desk review of official sources

EU/EEA country recommendations for the use of Vaxzevria

As of 12 May 2021, 15 EU/EEA countries have adopted specific recommendations to administer Vaxzevria only to certain age groups, in most cases (13 countries) to elderly people above a certain age (for the elderly the age limit varies across countries between ≥ 50 years and ≥ 65 years). In one country (Bulgaria) specific age recommendations apply for women only.

Twelve countries recommend the use of Vaxzevria based on EMA's current Summary of Product Characteristics (SmPC) - i.e. in people aged 18 years and above [29]. However, for some countries certain exceptions are applied, such as for pregnant women (three countries), and for those with a history of thromboembolic events or risk factors for such events (five countries). Three of these countries (Spain, Poland and Malta) also have an upper age limit for Vaxzevria administration (70 years of age). In France, the use of mRNA-based vaccines is recommended in areas with high circulation of B.1.351, due to reports of Vaxzevria having lower vaccine effectiveness on this variant. In some countries, individuals outside the recommended age interval can obtain Vaxzevria on a voluntary basis, based on an individual assessment of risk-benefit. In Slovakia, the use of Vaxzevria as a first vaccination dose has been discontinued and the vaccine will only be used to complete the vaccination schedule for those who have already received it as a first dose [30].

At national level, the decisions on discontinuation or recommendations and restrictions on the use of Vaxzevria have been based on the SmPC for Vaxzevria; risk-benefit analysis and expert opinion, using safety data from EMA and notification of local cases of TTS; the observed versus expected occurrence of TTS; national data on risk of death or ICU admission due to COVID-19 by age, and the national epidemiological situation. Availability of other COVID-19 vaccines has also been taken into consideration in the decision-making process.

EU/EEA country recommendations for the second dose after a first dose of Vaxzevria

As regards recommendations on the administration of a second dose of COVID-19 vaccine to those who already received a first dose of Vaxzevria, as of 12 May 2021 the situation is as follows:

- A total of 20 EU/EEA countries currently recommend the administration of a second dose of Vaxzevria, with the exception of individuals who had reactions to the first dose or had thromboembolic events (two countries). This includes seven countries with revised recommendations in terms of age restriction, but where the second dose of Vaxzevria is recommended to all individuals who received the first, irrespective of their age.
- Five countries have revised their recommendations and will administer the second dose with an mRNA vaccine (Comirnaty by BioNTech/Pfizer or COVID-19 Vaccine Moderna).
- In four countries, the decision on the second dose is still under consideration, as the expected administration of the second dose of Vaxzevria would only begin in late May 2021. Further evidence is being reviewed or expected to become available, including evidence from ongoing 'mix and match' studies and data from the United Kingdom, where vaccination with Vaxzevria has been further expanded, including the administration of the second dose.

In countries that have adopted specific age restrictions, the decision to still administer a second dose of Vaxzevria, irrespective of age, was motivated by the consideration that there was a low probability of TTS occurring after the second dose if it did not occur after the first one. Another factor taken into consideration was the lack of evidence on the effectiveness of mixed vaccine schedules.

Countries reported that the decision for using an mRNA vaccine for the second dose in individuals who received a first dose of Vaxzevria was mainly based on previous experience and data on heterologous boosting with other antiviral vaccines (e.g. HIV, hepatitis B or C, HPV, influenza and Ebola virus) [31,32]. This takes into consideration the fact that vaccines against SARS-CoV-2, regardless of the platform, are targeting the same antigen (spike protein). It also takes into consideration evidence from studies conducted in animal models, testing prime boost heterologous strategies combining adenoviral vector and mRNA vaccines, where a strengthened immune response was found [33,34]. The analogy with the immunogenicity of a single dose vaccination in SARS-CoV-2 sero-positive individuals (i.e. previously infected persons) was also mentioned.

Countries highlighted that accurate data on the risk of TTS following vaccination with Vaxzevria and related death by age and sex (i.e. not just number of events, but also denominators corresponding to the number of vaccine doses administered by age and sex) are needed for more granular risk-benefit analysis and decision making. More data on 'mix and match' schedules and vaccine efficacy on variants of concern (e.g. B.1.351) are also required.

Table 1. National recommendations for the use of Vaxzevria in EU/EEA countries (as of 12 May 2021)*

Country	Current recommendations for use of Vaxzevria	Recommendations for second dose	Comments
Austria	Based on the SmPC	Vaxzevria	Added advice to physicians on the use of medications and information for those vaccinated.
Belgium	≥41 years of age	Vaxzevria	Anyone who has already received a first dose will also receive a second dose after 12 weeks.
Bulgaria	Based on the SmPC (see exceptions in comments)	Vaxzevria	Not to be used in women under 60 years of age with increased risk of thrombosis and/or history of thrombocytopenia.
Croatia	Based on the SmPC	Vaxzevria	
Cyprus	Based on the SmPC	Vaxzevria	If no reaction to the first dose, a second dose of Vaxzevria can be given.
Czechia	Based on the SmPC	Vaxzevria	
Denmark	Discontinued	mRNA vaccine	
Estonia	≥50 years of age	Vaxzevria	The NITAG concluded that there is no evidence available for using another vaccine or technology. Experts concluded it is very unlikely that a similar reaction would occur with the second dose if it did not occur with the first, taking into account the evidence available on the mechanism of the thromboembolic events.
Finland	≥65 years of age (see exceptions in comments)	mRNA vaccine	Those with previous CVST or atypical heparin-induced thrombocytopenia (aHIT) should not receive Vaxzevria. Recommendations will be revisited once more data become available.
France	≥55 years of age (see comments)	mRNA vaccine	An mRNA vaccine is preferred for pregnant women. In areas with high circulation of B.1.351, mRNA is recommended.

Country	Current recommendations for use of Vaxzevria	Recommendations for second dose	Comments
Germany	≥60 years of age	mRNA vaccine	The use of Vaxzevria for a first or second dose below this age limit, however, remains possible at the discretion of the doctor, based on comprehensive information and individual risk acceptance.
Greece	≥30 years of age	Vaxzevria	Second doses expected to start on 13 May 2021. Final recommendations for the second dose are pending.
Hungary	Based on the SmPC	Vaxzevria	
Iceland	60-69 years of age	Under consideration	Avoid in women under 55 years, people with history of spontaneous thrombosis, myelodysplastic syndromes and certain other conditions with high risk of thrombosis. Awaiting data from the UK for decision on second dose.
Ireland	≥60 years of age	Under consideration	Extended period for second dose to 16 weeks to allow for more data on mixed schedules to be available.
Italy	≥60 years of age	Vaxzevria	
Latvia	Based on the SmPC (see comments)	Vaxzevria	Not recommended for pregnant women (if risk factors are high, pregnant women may be vaccinated) because of possible difficulties in differentiating pregnancy pathologies from TTS-like symptoms (aHIT) both clinically and in the laboratory.
Lithuania	Based on the SmPC	Vaxzevria	
Liechtenstein	Vaxzevria not in use		
Luxembourg	≥55 years of age (see comments)	Vaxzevria	Pregnant women should be given mRNA vaccine. For people aged 30-54 years at risk of severe COVID-19, preference should be given to mRNA vaccines, if available. Benefit-risk estimation for healthy people used to determine restrictions in Vaxzevria use.
Malta	18-70 years of age	Vaxzevria	
Netherlands	≥60 years of age	Vaxzevria	Vaccine induced prothrombotic immune thrombocytopenia (VIPIT) is contraindication.
Norway	Discontinued	Under consideration	
Poland	Based on the SmPC (see comments)	Vaxzevria	People who have had a documented or probable heparin-induced thrombocytopenia (HIT) in the past, or who were confirmed CVST should be vaccinated against COVID-19 with mRNA vaccine.
Portugal	≥60 years of age	Vaxzevria	
Romania	Based on the SmPC	Vaxzevria	People who developed vein thrombosis after the first dose of Vaxzevria will not receive the second dose with the same vaccine.
Slovakia	Vaxzevria discontinued as first dose.	Vaxzevria	Vaxzevria will be used as a second dose to complete the vaccination course for those that received it as a first dose. As of 11 May 2021, Vaxzevria will not be used as a first dose.
Slovenia	Based on the SmPC	Vaxzevria	An mRNA vaccine is preferred for pregnant women.
Spain	60-69 years of age	Under consideration	Extended period for second dose, for those <60 years of age previously vaccinated with one dose, to 16 weeks to allow for more data on mixed schedules to be available.
Sweden	≥65 years of age	mRNA vaccine	

* This table has been updated to reflect the fact that Belgium is now also recommending the administration of Vaxzevria as a second dose. (18 May 2021)

Note: information in the table provided from the following sources: survey results, presentations from country experts, ad hoc consultation with EU/EEA countries, and official public health authority websites.

SmPC: EMA summary of product characteristics [29]

Options for the second dose and supporting evidence

Some EU/EEA countries have decided to restrict use of Vaxzevria to specific age groups and/or to wait for evidence to guide future decisions on full vaccination (and effective protection against COVID-19) for those having already received a first dose. Therefore available evidence has been assessed with a view to the following options for the administration of the second dose:

- second dose of Vaxzevria to everyone that received a first dose of Vaxzevria;
- completion of the vaccination schedule with an mRNA vaccine;
- completion of the vaccination schedule with another adenovirus-vector based vaccine;
- no additional dose administered.

These options may apply in situations where a recommendation has been issued by national authorities to restrict the use of Vaxzevria to certain age or population groups, or where a decision has been taken to delay the second dose beyond the recommended time interval.

A summary of the current evidence for each option is presented below to inform EU/EEA countries when taking decisions on the administration of the second vaccine dose following a first dose of Vaxzevria, depending on their local context.

Second dose of Vaxzevria to everyone that received the first dose

This recommendation is supported by EMA's CHMP. In their communication dated 23 April 2021, CHMP recommended 'to continue giving a second dose of Vaxzevria between four and 12 weeks after giving the first one in line with the product information'. As of yet, there is no evidence of the risk of TTS after the second dose of Vaxzevria. The Committee concluded that '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' [12].

However, based upon national risk-benefit assessments and the availability of alternative COVID-19 vaccines, some Member States have decided to discontinue using Vaxzevria, as per the product information, and are instead restricting or recommending the vaccine to specific population groups, as summarised Table 1 above.

Real-life data from vaccine roll-out will be important in order to guide future decisions. As of 5 May 2021, the UK has vaccinated 7.5 million individuals with two doses of Vaxzevria, with an occurrence of eight TTS cases after the second dose. This is against the context of a total 23.3 million doses (both first and second) of Vaxzevria administered in the UK, with an estimated 10.9 TTS cases per million doses. However, the UK Yellow Card data (the system used for collecting and monitoring information on safety concerns involving medicines or medical devices in the UK) described above cannot be used to derive side effect rates or compare the safety profile of COVID-19 vaccinations as many factors can influence adverse drug reaction (ADR) reporting [35].

Completion of the vaccination schedule with an mRNA vaccine

There is some evidence on the immunogenicity, safety and efficacy of mixed schedules from clinical trials, and also some trials ongoing, as detailed below. A good immune response could be expected from combining different COVID-19 vaccines, as all licensed vaccines induce an immune response against the SARS-CoV-2 spike protein, and it is expected that mixing vaccines could potentially boost immune responses in the process [36].

Due to the TTS signal following vaccination with Vaxzevria, some EU/EEA countries have started recommending a second dose of an mRNA vaccine (Comirnaty or COVID-19 Vaccine Moderna) to individuals who received a first dose of Vaxzevria. In communication with EU/EEA countries and the survey mentioned above, some of the arguments and evidence put forward include the following:

- Data acquired from the development of other antiviral vaccines. Heterologous prime-boost strategy is widely studied in the context of the development of many vaccines including HIV vaccines (where it aims to induce a T lymphocyte response), hepatitis B or C vaccines, HPV and influenza vaccines, and more recently studies leading to the marketing authorisation of two vaccines against Ebola virus [31,32].
- Vaccines against SARS-CoV-2, irrespective of the platforms, are targeting the same antigen (spike protein).
- Studies conducted in animal models, where they tested prime boost heterologous strategies combining adenoviral vector and mRNA vaccines, indicated a strengthened immune response [33,34].
- Similar concept to vaccinating SARS-CoV-2 sero-positive individuals - i.e. studies on single-dose vaccination in previously-infected persons.

A clinical trial was launched in the UK (Com-Cov) [37] in February 2021 to assess the immune response, efficacy and safety of a mixed COVID-19 vaccine schedule. During the first stage, Vaxzevria was given, followed by Comirnaty, and vice versa, with four- or 12-week dosing schedules. In April, the trial was expanded to include the Moderna COVID-19 Vaccine and NVX-CoV2373 by Novavax. The study will run for a year. Initial reactogenicity and safety data was recently published. The outcome of this study indicates a less favourable safety profile for a heterologous schedule compared to an autologous schedule. Some of the key features are set out below.

- There was an increase in systemic reactogenicity self-reported solicited local and systemic symptoms collected in the seven days after both prime and boost vaccination in heterologous vaccine schedules in comparison to homologous vaccine schedules.
- Feverishness was reported by 37 (34%) of 110 recipients of Vaxzevria for prime and Comirnaty for boost compared with 11 (10%) of 112 recipients of Vaxzevria for both prime and boost (difference 24%, 95% CI 13-35%).
- While similar increases were observed for chills, fatigue, headache, joint pain, malaise, and muscle ache, no hospitalisations occurred due to these symptoms, which were mostly observed in the 48 hours after immunisation.

The study will run for a year and a more complete safety dataset and immunogenicity results for heterologous prime-boost schedules is expected to be published in June 2021 [38]. AstraZeneca has also announced that there will be a mix-and-match dosing trial with the Sputnik V vaccine, to be conducted in Azerbaijan [39]. In France, a cohort study will be conducted in individuals vaccinated with Vaxzevria followed by an mRNA vaccine in order to assess the immune response conferred by this vaccination regimen, with specific monitoring through pharmacovigilance [40]. In Spain, a mix and match study in individuals vaccinated with Vaxzevria who receive a second dose with Comirnaty is also being planned as per official communication [41].

Completion of the vaccination schedule with another adenovirus-vector based vaccine

As yet, there is no data on the immunogenicity, safety and efficacy of the use of another adenovirus-vector based COVID-19 vaccine as a second dose in a mixed schedule. Currently, the only other such vaccine authorised for use in the EU is the COVID-19 Vaccine Janssen, which is administered as a one-dose regimen [42], and also possibly linked to very rare TTS events [13]. To date, no EU/EEA country has adopted a strategy of completing the vaccination schedule with another adenovirus-vector based vaccine.

No additional dose administered

This scenario refers to both the administration of a single dose of Vaxzevria ('one-dose' regimen) and a delayed second dose. Reasons for delaying the second dose could be related to vaccine supply and the public health objective of ensuring initial protection, conferred by a first vaccine dose, to as many as possible of those at risk or, as described above, in order for more evidence on adverse effects, risk factors, or effectiveness of mixed schedules to emerge. Many countries have extended the time between the first and the second dose to enable provision of first doses to as many people in the priority groups as possible while there were a limited number of vaccines available [2].

Vaxzevria is not licensed for a one-dose schedule and is indicated to be administered as two standard doses, the second dose between four and 12 weeks after the first dose to ensure adequate, long-term protection [29]. Evidence that has emerged from both clinical trials and post-licensing studies on the immunogenicity and protection conferred after the first dose of Vaxzevria, in a two-dose schedule at various endpoints and with different follow-up periods, is summarised below.

Evidence from clinical trials

A pooled analysis of four randomised trials on the immunogenicity and protection of a single-dose administration of Vaxzevria showed that vaccine efficacy after a single standard dose of vaccine from day 22 to day 90 after vaccination was 76.0% (59.3–85.9), with minimal waning of antibody levels by day 90 (geometric mean ratio [GMR] 0.66 [95% CI 0.59–0.74]) [29].

Evidence from post-licensing studies

Several studies are investigating the effectiveness of one dose in a two-dose schedule against infection as the main outcome. In the UK, a study investigated the impact of vaccine administration on COVID-19 infection and possible virus transmission by assessing rates of positive testing after single-dose vaccination. The study found that at 28 days after one dose of vaccination there was a 74% (HR 0.26 (0.19-0.35)) reduction in risk of testing positive for COVID-19 for individuals that had received Vaxzevria, compared to unvaccinated individuals [43]. A UK cohort study, published as a preprint, UK compared vaccine effectiveness of a first dose of either Vaxzevria or Comirnaty against infection in long-term care facility (LTCF) residents in England. Researchers found that both vaccines were associated with substantially reduced SARS-CoV-2 infection risk in LTCF residents (median age 86 years) from four weeks to at least seven weeks. There was similar protection from both vaccine types, with the effect of the first dose estimated to be 56% (19–76%) at 28–34 days, and 62% (23–81%) at 35–48 days following a single dose of Vaxzevria or Comirnaty [27]. An observational cohort study in UK healthcare workers investigated protection from symptomatic and asymptomatic infection conferred by vaccination after one and two doses of either Vaxzevria or Comirnaty. The study found that single-dose vaccination up to 42 days after vaccination reduced the incidence of symptomatic infection by 67% (0.33[0.21-0.52]) and any asymptomatic infection by 64% (0.36[0.26-0.50]) (based on pooled analysis from Vaxzevria and Comirnaty vaccines) [44]. A UK cohort study (preprint) assessed the effectiveness of vaccination in preventing infection in the community and reported that, with a single dose of Vaxzevria or Comirnaty, the odds of new infection were reduced by 65% (95% CI 60 to 70%; $P < 0.001$) in the ≥ 21 days from first vaccination with no second dose compared to unvaccinated individuals with no prior infection. In those vaccinated, the largest reduction in odds was seen after the second dose (70%, 95% CI 62 to 77%; $P < 0.001$) [45].

Other studies measure the effectiveness of one dose in a two-dose schedule against severe disease. In the UK, a study estimating the real-world effectiveness of Vaxzevria against confirmed COVID-19, hospitalisations and deaths in adults aged 70 years or older found that effectiveness was seen between 14 and 20 days after vaccination, reaching 60% (95%CI 41-73%) from 28–34 days and further increasing to 73% (95% CI 27-90%) from day 35 after vaccination. Cases vaccinated with one dose of Vaxzevria had an additional 37% (95% CI 3-59%) lower risk of emergency hospitalisation. There was insufficient follow-up to assess the effect of Vaxzevria on mortality due to the later roll-out of this vaccine. Combined with the effect against symptomatic disease, the study results indicate that a single dose of Vaxzevria is approximately 80% effective at preventing hospitalisation [26].

In the UK, a large prospective cohort study (Lancet preprint) using linked database records of the population in Scotland showed that a single dose of the Vaxzevria resulted in substantial reductions in the risk of COVID-19 related hospitalisation, with an estimated effectiveness of 94% (95% CI 73 to 99) of the first dose in preventing hospital admissions at 28–34 days post-vaccination. In those aged ≥ 80 years there was a vaccine effectiveness of 81% against hospitalisations (with pooled data from AstraZeneca and Pfizer/BioNTech vaccines) and the effectiveness increased over time [28].

A case control study (Lancet preprint) in England assessed the effectiveness of Vaxzevria and Comirnaty in preventing hospitalisations in individuals aged 80 years and over. The study found that first dose effectiveness against hospital admissions for Vaxzevria was 80.4% (95% CI 36.4-94.5) between 19 and 64 days after vaccination. Authors concluded that a single dose of Vaxzevria resulted in substantial reductions in the risk of COVID-19-related hospitalisation in elderly, frail patients with extensive co-morbid disease [46].

Effectiveness of one dose against transmission in a two-dose schedule was investigated in a register-based analysis from Scotland looking at the effectiveness of COVID-19 vaccine against transmission of SARS-CoV-2 to susceptible contacts from vaccinated cases. This analysis has shown that household members of healthcare workers vaccinated with a single dose of either Vaxzevria or Comirnaty (results based on pooled analysis) were at significantly reduced risk (HR=0.70; 95% CI: 0.63–0.78) of PCR-confirmed SARS-CoV-2 infection, and non-statistically significant reduced risk of hospitalisation (0.77; 95% CI: 0.53-1.10), compared to household members of unvaccinated healthcare workers, 14 days after vaccination [47].

A UK preprint study assessing real-world data on antibody response post-vaccination in the general population found that seroconversion rates and quantitative antibody levels after a single dose of Vaxzevria and Comirnaty were lower in older individuals, especially those aged >60 years. Two doses achieved high responses across all ages, with older people having significantly increased seropositivity and antibody levels, whereas the incremental increase in younger participants aged 20–40 years with second vaccine was smaller in the short term. Based on these results, the authors suggest that vaccines should be prioritised for those not previously infected, and second doses prioritised for individuals aged >60 years when vaccine supplies are limited [48].

A UK study looking at the timing of administration of a second dose Vaxzevria found that the vaccine is efficacious, with results varying by dose interval in exploratory analyses. Vaccine efficacy after a single standard dose of Vaxzevria from day 22 to day 90 after vaccination was 76.0% (59.3–85.9) which, according to a modelling analysis, did not wane during a three-month period. Antibody levels were also maintained during this period. Vaccine efficacy was higher in those participants that received the second dose with a longer interval (vaccine efficacy 81.3% [95% CI 60.3–91.2] at ≥ 12 weeks) than in those with a short interval (vaccine efficacy 55.1% [33.0–69.9] at <6 weeks). Binding antibody responses were more than two-fold higher after an interval of 12 or more weeks, compared with an interval of less than six weeks in those aged 18–55 years (GMR 2.32 [2.01–2.68]) [49].

Although studies are emerging on the protective effect of a single dose of COVID-19 vaccines authorised for use with a two-dose schedule, there is a substantial knowledge gap on the duration of protection. Follow-up periods after one dose are limited as studies were primarily investigating the interval between the first and second dose. The efficacy and effectiveness of one dose versus two doses has not been studied at length. Further evidence on duration of protection after one dose of Vaxzevria is needed.

Other considerations

Since pregnancy predisposes to thrombosis, and because pregnancy pathologies can be difficult to differentiate from TTS-like symptoms (aHIT) but are treated very differently, many EU/EEA countries have opted not to use Vaxzevria in pregnant women. However, risk-benefit assessment at individual level, as well as the availability of other vaccines, should be taken into consideration. A recently published study from the US involving 36 591 pregnant women found no obvious safety signals among pregnant women who received mRNA COVID-19 vaccines [50]. While clinical trials did not include pregnant women on a large scale, available data, mainly from the US vaccine roll-out, do not indicate any adverse effect on pregnancy [51]. The latest advice from the UK Joint Committee on Vaccination and Immunisation (JCVI) is that COVID-19 vaccines should be offered to pregnant women at the same time as the rest of the population, based on their age and clinical risk. Since Comirnaty and Moderna COVID-19 Vaccine have been studied more extensively in pregnant women, the advice is that these are preferred for pregnant women in the UK. However, pregnant women who have received a first dose of Vaxzevria are recommended to complete the course with the same vaccine [52].

Table 2. Summary of options and supporting evidence

Options for the second dose	Supporting evidence		
	Evidence available in the approval dossier (source: EMA EPAR ¹)	Published evidence	Is additional evidence being gathered?
Second dose with Vaxzevria to all those who received the first dose	Current licensing based on two-dose schedule. As per SmPC for Vaxzevria: 'a full vaccination course consists of two doses of vaccine with an interval of between four and 12 weeks (28 to 84 days) after the first dose.'	Limited evidence available on risk of TTS after second dose. Available risk-benefit analysis (EMA and the UK) show that the benefits of vaccination in terms of averted hospitalisations, ICU admissions and deaths, rise as age and infection rates increase. The benefits of Vaxzevria outweigh its risks in adults of all age groups, despite the very rare cases of TTS following vaccination. Early data from the UK roll-out indicate a lower risk of TTS following second dose of Vaxzevria. At present there are no, or limited data to guide a change in current recommendations.	Safety is being monitored throughout the EU/EEA and benefit risks assessments are being undertaken on an ongoing basis by national regulatory authorities as evidence accumulates. Further UK data on TTS after second dose from vaccine roll-out pending.
Completion of the vaccination schedule with an mRNA vaccine	This option is currently not supported by the evidence available at licensing. As per SmPC for Vaxzevria: 'there are no data available on the interchangeability of Vaxzevria with other COVID-19 vaccines to complete the vaccination course. Individuals who have received the first dose of Vaxzevria should receive the second dose of Vaxzevria to complete the vaccination course.'	Limited data on effectiveness of mixed vaccine schedules, however: same viral protein targeted with mRNA vaccine and therefore a boost in pre-existing immunity expected. A strengthened immune response was found in studies conducted in animal models testing prime boost heterologous strategies combining adenoviral vector and mRNA vaccines. No data on safety in a mixed schedule however, good safety profile of mRNA vaccines to date. Local and systemic safety data was recently published for a mixed schedule. The outcome of this study indicated a less favourable safety profile of heterologous schedule compared to an autologous schedule.	Yes, ongoing mix and match studies in some EU/EEA Member States and the UK. Some EU/EEA Member States are recommending mRNA vaccine in a mix-match schedule.
Completion of the vaccination schedule with another adenovirus-vector based vaccine	This option is currently not supported by the evidence available at licensing. As per SmPC for Vaxzevria: 'there are no data available on the interchangeability of Vaxzevria with other COVID-19 vaccines to complete the vaccination course. Individuals who have received the first dose of Vaxzevria should receive the second dose of Vaxzevria to complete the vaccination course.'	No data on effectiveness when used as second dose in a mixed schedule. The only other adenovirus-vector based vaccine licensed in the EU (COVID-19 Vaccine Janssen) is licensed for use in a one-dose schedule. No safety data when both vaccines are used in a mixed schedule. The COVID-19 Vaccine Janssen safety is currently being investigated.	Not to date.
No additional dose provided	This option is currently not supported by the evidence available at licensing. A one-dose regimen is not expected to provide full and long-term protection against COVID-19. Approved vaccine regimen as per Vaxzevria SmPC: 'a full vaccination course consists of two doses of vaccine with an interval between four and 12 weeks (28 to 84 days) after the first dose.'	There is evidence of high immunogenicity and efficacy against symptomatic COVID-19 for 90 days following a single dose of Vaxzevria in clinical trials. Effectiveness studies of a single dose of Vaxzevria show: <ul style="list-style-type: none"> highly immunogenic in previously naïve vaccine recipients (follow up 32 days) substantial reduction in risk of infection (follow-up 48 days) substantial reduction in risk of severe disease (hospitalisation) (follow-up 64 days) Limited data available on providing only one dose: <ul style="list-style-type: none"> Unsure of length of protection with only one dose and the potential for waning immunity (limited to follow-up times after one dose of vaccination, majority of studies were looking at interval between first and second dose, not at immunogenicity, efficacy and effectiveness of one dose vs two doses). Further evidence is needed on duration of effect. Clinical studies have shown that a second dose induces increased neutralising antibody levels. The effect that variants of concern may have on vaccine efficacy and immune responses (researchers currently looking into different boosting schedules). 	

¹ https://www.ema.europa.eu/en/documents/product-information/vaxzevria-previously-covid-19-vaccine-astrazeneca-epar-product-information_en.pdf

Discussion

COVID-19 vaccine rollout is progressing, but EU/EEA countries still face challenges in terms of vaccine supply. Vaccine uptake is still low in the adult population, even though it is higher in target groups, such as the elderly and healthcare workers, in most countries. Vaxzevria represents approximately 24% of the vaccine doses supplied in the EU/EEA and 19% of the doses administered since the beginning of the rollout.

The safety signal from episodes of TTS after administration of Vaxzevria has probably affected the use of supplies in many countries (observed reduction in proportion of doses of Vaxzevria used in week 13, 2021) and many countries have been updating their recommendations, including adding age-based restrictions for its use. Providing clear guidance to professionals on follow-up vaccination of individuals who received a first dose of Vaxzevria is important in order to avoid leaving part of the population inadequately vaccinated.

During week 17, 2021, almost 80% of the Vaxzevria doses administered were to persons aged >60 years – where the benefits are higher according to age-based risk benefit assessments by the EMA [13] and the UK [53]. EMA's CHMP also concluded that the benefits of vaccination in terms of averted hospitalisations, ICU admissions and deaths, rise as age and infection rates increase. However, in the context of limited supplies, restricting use of Vaxzevria for older age groups may cause a delay in vaccination programmes, once vaccine coverage in older age groups increases and roll-out moves on to younger age groups. In addition, considering that many countries have adopted age restrictions for the administration of Vaxzevria and that the cumulative uptake in the elderly is increasing in many countries, there might be overstocking or wastage of Vaxzevria doses in some countries in the future. Furthermore, the signal could have a potential impact on vaccine hesitancy towards Vaxzevria, with some countries reporting a lowering acceptance of this vaccine [1]. Based on results from the survey sent out to the EU/EEA NITAGs, most countries either have strategies in place or are working on ways in which to address vaccine hesitancy due to Vaxzevria safety concerns.

Important factors that should be considered in a risk-benefit analysis on the use of Vaxzevria are the local epidemiological situation and the availability of other COVID-19 vaccines. These factors will influence the public health impact (in terms of severe cases, ICU admissions and death from COVID-19) of a potential delay in a vaccination programme due to restricted use of Vaxzevria. In countries where community transmission is low and where availability of other COVID-19 vaccines is high, the public health impact will be lower than in countries where transmission is high and vaccine uptake is likely to be affected by delayed or restricted use of Vaxzevria.

Conclusions

Four possible scenarios have been considered in this report for the administration of a second dose of COVID-19 vaccine after a first dose of Vaxzevria:

- Vaxzevria as a second dose for all those who received the first dose;
- mRNA COVID-19 vaccine as a second dose;
- another adenovirus vector vaccine as a second dose;
- no second dose or delayed interval between dose one and dose two.

At present, the empirical data available to guide a change in recommendations are limited. TTS remains a serious but very rare side effect of Vaxzevria, against which the public health impact of delayed vaccination programmes due to changed recommendations for Vaxzevria usage need to be assessed. This risk-benefit analysis will differ for countries and individuals, and needs to take into account the local epidemiological situation and availability of other authorised COVID-19 vaccines.

The evidence relevant to decisions on the options outlined above is limited or currently absent. The existing evidence and the gaps in evidence include:

- There is a substantial knowledge gap on the duration of protection for a single dose of Vaxzevria. The follow-up period after one dose is limited as studies have primarily investigated the interval between the first and second dose. However, some studies indicate a protective effect of Vaxzevria for a longer period than the current dosing interval recommendations, which could support increasing the dosing interval to allow further evidence to emerge.
- Evidence on mixed vaccine schedules is currently limited. Local and systemic reactogenicity data of a mixed schedule has recently been published. The outcome of this study indicated a less favourable safety profile for a heterologous schedule than an autologous schedule.
- All COVID-19 vaccines currently authorised for use in the EU/EEA target the same protein (S-protein), rendering it probable that the vaccine effectiveness would continue to be high for a mixed vaccine schedule, which is supported by studies using animal models.
- The benefit/risk ratio of Vaxzevria rises with age and infection rates, and decisions on usage need to be placed in the context of the public health impact of changing the recommendations for use and thereby potentially delaying vaccine rollout.

- Evidence for an increased or decreased risk of developing TTS after a second dose of Vaxzevria is lacking, as is evidence on the safety and effectiveness of mixed vaccination schedules and whether there are brand-specific differences in vaccine effectiveness with regard to variants of concern

Preliminary data from the UK vaccine roll-out suggest a lower rate of TTS after administration of a second dose compared to the first dose of Vaxzevria. Further exposure and a longer follow-up period is needed to determine whether the risk of TTS after a second dose of Vaxzevria will differ from the risk after the first dose. It will be important to follow-up cohorts vaccinated in a mixed vaccination schedule (i.e. an mRNA vaccine as second dose) in order to document the efficacy and safety of such a vaccine regimen. EU/EEA countries are therefore encouraged to implement cohort studies. A mixed schedule could also add some flexibility to the vaccine roll-out and potentially contribute to improved protection, although this is yet to be confirmed by evidence.

The benefits of Vaxzevria rise as age and infection rates increase and decisions on usage need to be put into the context of the public health impact of restricting the recommendations for its use, thereby potentially delaying the overall vaccine roll-out. At present, there are no or limited data available to support any alternative approach to the current recommendations included in EMA's SmPC. The risk-benefit analysis and decisions on the second dose may therefore differ across countries, depending on the local epidemiology and availability of COVID-19 vaccine supplies.

Limitations

This assessment is based on facts known to ECDC at the time of publication.

- The investigation of safety is still ongoing. There is limited data on TTS after a second dose of Vaxzevria, due to the timeline of the vaccine roll-out.
- There is a lack of evidence from initial clinical trials on duration of protection from one dose and on mixed schedules. Studies regarding mixed vaccination schedules are ongoing, but results are not available yet.
- There is little know about the effect that variants of concern may have on vaccine efficacy and immune responses and further scientific evidence is needed.
- The policy landscape is rapidly changing, based on new evidence becoming available and NITAG decisions at the national level are changing accordingly.

Contributing ECDC experts (in alphabetical order)

Kim Brolin, Tarik Derrough, Kate Olsson, Lucia Pastore Celentano, Giovanni Ravasi

External reviewers

The following external reviewers provided helpful reviews of the document. All experts have submitted declarations of interest, and a review of these declarations did not reveal any conflict of interest.

Marco Cavaleri, European Medicines Agency (EMA); Hester de Melker, RIVM Netherlands; Aurora Limia, Ministry of Health, Spain; Marta Vitek, National Institute of Public Health, Slovenia.

All experts have submitted declarations of interest, and a review of these declarations did not reveal any conflict of interest.

Disclaimer

All data published in this report is correct to the best of our knowledge at the time of publication.

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Annex1. Request for information on current use of Vaxzevria AstraZeneca in EU/EEA countries

Dear NITAGs Collaboration Members,

The ECDC is in the process of developing a short technical report on the current evidence and scientific rationale on the use of Vaxzevria AstraZeneca in different population groups and the administration of a second COVID-19 vaccine dose in individuals previously vaccinated with Vaxzevria, especially in countries where the use of this product has been suspended.

We kindly ask you to respond to this brief request for information by Wednesday 14 April 2021 at 12:00.

Name of the person completing this form	
Date	
Country	

1. What is the current recommendation for the use of Vaxzevria in your country? <i>(Please include link of the most updated protocol or recommendation)</i>	
2. Was there a change to the recommendations on the use of Vaxzevria in light of temporal association with thromboembolic events? <i>(If yes, please briefly describe the change in the recommendation).</i>	(No/Yes)
3. Is any age restriction in place for the use of Vaxzevria? <i>(If yes, please, specify age cut-off)</i>	(No/Yes)
4. If an age restriction was adopted, what rationale was used to define the age cut-off? <i>(Please include any analysis conducted at national level on the benefit-risk by age and other variables of interest; please include any relevant report and methodology)</i>	
5. Is any other restriction in place for the use of Vaxzevria other than age (e.g. gender; specific population groups, etc.)? <i>(If yes, please, briefly specify the other restrictions in place)</i>	(No/Yes)
6. If other restrictions were adopted, what rationale was used to define them? <i>(Please include any analysis conducted at national level on the benefit-risk by age and other variables of interest; please include any relevant report and methodology)</i>	
7. What is the current recommendation for the administration of the second dose of COVID-19 vaccine in individuals who previously received a first dose of Vaxzevria? <i>(Please, share any relevant reference on the scientific rationale for the current recommendation).</i>	
8. Considering the thromboembolic events under surveillance temporally associated with Vaxzevria, please share: <ul style="list-style-type: none"> any case definition(s) currently used for monitoring these events at national level data collection forms for investigating and reporting these events <i>(Please include link or attach file in your response).</i> 	
9. Please share any publicly available safety reports on thromboembolic events temporally associated with Vaxzevria <i>(Please include link or attach file in your response).</i>	
10. Are there any communications strategies and plans in place to address possible vaccine hesitancy towards Vaxzevria? <i>(If yes, please briefly specify)</i>	(No/Yes)