16 September 2021
EMA/530434/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure under Article 5(3) of Regulation (EC) No 726/2004

Invented name: Vaxzevria

Active substance: Chimpanzee Adenovirus encoding the SARS-CoV-2 Spike glycoprotein (ChAdOx1-S)

Procedure number: EMEA/H/A-5(3)/1507

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Information on the procedure

Following the conclusion of a possible link between Vaxzevria (previously known as AstraZeneca vaccine) and very rare cases of unusual blood clots with low blood platelets (thrombosis in combination with thrombocytopenia (TTS)), the European Commissioner for Health and Food Safety requested a further analysis and stratification of data to be performed, to better characterise the benefit and risk of the vaccine in different age groups and/or sex, as well as possible other risk factors that could be identified. The European Medicines Agency was also requested to provide, if possible, a recommendation on the administration of the second dose of Vaxzevria on the basis of the available data.

On 9 April 2021 the European Commission (EC) therefore triggered a procedure under Article 5(3) of Regulation (EC) No 726/2004, and requested the Agency for a scientific opinion on the above issues, in order to inform national vaccination campaigns.

In order to support Member States, national medicines regulators and healthcare professionals, the European Commission requested the Agency to give its opinion – possibly in an interim form – by 22 April 2021.

2. Scientific discussion

2.1. Introduction

Vaxzevria is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of SARS-CoV-2. The SARS-CoV-2 S immunogen in the vaccine is expressed in the trimeric pre-fusion conformation; the coding sequence has not been modified to stabilise the expressed S-protein in the pre-fusion conformation. Following administration, the S glycoprotein of SARS-CoV-2 is expressed locally and stimulates neutralising antibody and cellular immune responses, which may contribute to protection against COVID-19.

Vaxzevria is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older; the use of this vaccine should be in accordance with official recommendations.

In March 2021, a signal assessment was initiated at PRAC for embolic and thrombotic events with Vaxzevria (previously COVID-19 Vaccine AstraZeneca). The review of data analyses from EudraVigilance (EV) with individual case review (EV search with cut-off date: 22 March 2021) and "observed versus expected" analyses, input from an ad hoc expert group and available literature pointed to signals of embolic and thromboembolic events, cerebral venous sinus thrombosis, splanchnic vein thrombosis and arterial thrombosis, with or without thrombocytopenia, mainly occurring in women below 60 years old, and with a time-to-onset within 2 weeks following vaccination.

On 7 April 2021, PRAC concluded that a causal relationship between vaccination with Vaxzevria and adverse events of thrombosis in combination with thrombocytopenia (TTS) was at least a reasonable possibility[1]. The product information was updated with information on thrombocytopenia and coagulation disorders to warn that *a combination of thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with Vaxzevria. This includes severe cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis, concomitant with*

[1] AstraZeneca's COVID-19 vaccine: EMA finds possible link to very rare cases of unusual blood clots with low blood platelets

thrombocytopenia. Some cases had a fatal outcome. The majority of these cases occurred within the first fourteen days following vaccination and occurred mostly in women under 60 years of age.

Healthcare professionals should be alert to the signs and symptoms of thromboembolism and or thrombocytopenia. Those vaccinated should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg swelling, persistent abdominal pain following vaccination. Additionally, anyone with neurological symptoms including severe or persistent headaches or blurred vision after vaccination, or who experiences skin bruising (petechia) beyond the site of vaccination after a few days, should seek prompt medical attention.

Further, thrombosis in combination with thrombocytopenia (thrombosis with thrombocytopenia syndrome - TTS) was added as an adverse drug reaction with the frequency very rare and thrombocytopenia with the frequency common.

As an outcome of this review, it was also decided to conduct a number of studies to identify the exact pathophysiological mechanism for the occurrence of these thrombotic events and better define the magnitude and characteristics of the risk. At that time, experience with exposure to the second dose of the vaccine was still limited with all cases of TTS reported after administration of the first dose of Vaxzevria.

On 9 April 2021, the EC triggered a procedure under Article 5(3) of Regulation (EC) No 726/2004, and requested the Agency to perform a further analysis and stratification of data to better characterise the benefits and risks of the vaccine in different age groups and/or sex, as well as possible other risk factors that could be identified. The EMA was also requested to provide, if possible, a recommendation on the administration of the second dose of Vaxzevria on the basis of the available data[2].

On 23 April 2021, the CHMP adopted an interim opinion further analysing and stratifying the data[3,4]. The analyses conducted showed that the benefits of vaccination increase with increasing age and increasing infections rates. However, it was not possible to further stratify risk by sex, as data on sex was received from only a subset of Member States (MSs) and it was not possible to validate extrapolation to the remaining MSs. The risk of TTS with Vaxzevria by sex could thus not be characterised, nor could possible other risk factors be identified.

In relation to the administration of the second dose of Vaxzevria, the CHMP concluded that two separate doses of Vaxzevria should be administered 4 to 12 weeks apart, in line with the product information. The mechanism behind the observed cases of TTS was unclear, and there had not been enough exposure and follow-up time to determine whether the risk of TTS with a second dose will differ from that of the first dose. For subjects that would not receive a second dose of Vaxzevria, there was no or limited data on alternatives for the administration of a second dose of Vaxzevria.

The present report focuses on further elucidating those aspects, as possible, based on data that has become available since the interim opinion.

2.2. Risk characterisation

The first aspect which the Agency was asked to consider was to contextualise the reports of TTS with the benefits of the vaccination by age and/or sex, as well as to identify possible additional risk factors for the occurrence of the TTS reactions.

[2] AstraZeneca's COVID-19 vaccine: EMA to provide further context on risk of very rare blood clots with low blood platelets
[3] Interim CHMP opinion under Article 5(3)
[4] Assessment report EMA/CHMP/214855/2021

In April 2021 the CHMP performed further analyses assuming different levels of effectiveness of the vaccine and different levels of TTS risk and stratifications of the data by age groups (see Appendix 1); however the data available did not allow to stratify the analyses by sex.

Since then, the results of an observational study describing incidence rates of thromboembolic events identified in primary care records databases became available. In addition, more detailed exposure data could be obtained from the MSs and further TTS cases were reported, including after the second dose of the vaccine. These data were evaluated with a view of further characterising the risk of TTS, if possible.

2.2.1. Observational study EUPAS40414

The subset of a European international network cohort study dedicated to thromboembolic events and thrombosis with thrombocytopenia after COVID-19 infection and vaccination, based on primary care computerised records from Catalonia (Spain; 426,272 Vaxzevria recipients – data up till 26th May 2021) and the UK (1,868,767 Vaxzevria (1st dose) vaccinees – data up till mid-March 2021) became available during the review. The CHMP sought the advice of the PRAC on the possibility to further characterise the risk of TTS further to vaccination with Vaxzevria based on those results (see also 3. Expert consultation).

The following results were noted in the UK database:

- Venous thromboembolism with thrombocytopenia: 7 observed vs 6.4 expected - SIR 1,09 [0,52-2,29]
- Arterial thromboembolism with thrombocytopenia: 5 observed vs 3,2 expected - SIR 1,57 [0,65-3,78]
- Sensitivity analysis of stroke with thrombocytopenia: higher observed (6 events) than expected (2,7 events) in the Vaxzevria cohort with SIR of 2.21 [0.99-4.91]. Equivalent to 3 excess cases in 1.9 million people vaccinated

In the Spanish database, TTS events were too rare to stratify (< 5 events).

The PRAC highlighted a number of limitations to the study, in particular, it was noted that TTS was very uncommon in this study and no statistically significant increase in risk was observed; due to the limited number of TTS cases, further stratification by e.g. sex or other risk factors or adjustment for confounders would not be meaningful or possible. The CHMP supported the limitations identified.

Results of a recent cohort study involving TTS patients (170 definite and 50 probable cases) in the UK[5], which found no sex preponderance and no identifiable medical risk factors, were also noted.

Based on the available data, the CHMP agreed with the PRAC that no new information could be identified to further characterise the risk of TTS following administration of Vaxzevria according to age groups or sex, or to identify risk factors.

[5] Pavord et al. Clinical Features of Vaccine-Induced Immune Thrombocytopenia and Thrombosis. NEJM, 2021. DOI: 10.1056/NEJMoa2109908

2.2.2. EEA incidence rates of TTS 30 days after the first and second dose of Vaxzevria

Data sources

Vaccination coverage data from the MSs obtained either directly or through European Centre for Disease Prevention and Control (ECDC)[6] (data cut off: 11 July 2021), were used to further analyse TTS cases reported to EV, the European database of reports of suspected adverse drug reactions.

In order to identify all cases of TTS, search was performed in EV (data cut off: 18 July 2021) with the MedDRA SMQ 'Embolic and thrombotic events' and specific preferred terms (PTs: acquired amegakaryocytic thrombocytopenia, anti-platelet antibody, autoimmune heparin-induced thrombocytopenia, heparin-induced, thrombocytopenia, heparin-induced thrombocytopenia test, heparin-induced thrombocytopenia test positive, immune thrombocytopenia, megakaryocytes abnormal, megakaryocytes decreased, non-immune heparin associated thrombocytopenia, platelet aggregation abnormal, platelet anisocytosis, platelet count, platelet count abnormal, platelet count decreased, platelet disorder, platelet maturation arrest, platelet production decreased, platelet toxicity, plateletcrit abnormal, plateletcrit decreased, spontaneous heparin-induced thrombocytopenia syndrome, thrombocytopenia, thrombocytopenia neonatal, thrombocytopenic purpura, thrombotic thrombocytopenic purpura) with COVID-19 VACCINE ASTRAZENECA (CHADOX1 NCOV-19).

Cases were identified based on structured reporting and were not subjected to individual case causality assessment.

Importantly it should be noted that there is no standardised way of reporting cases to EV as having occurred after the second dose of the vaccine. An *ad-hoc* search strategy was used to look through the structured fields where this information is most likely to be reported (excluding case narrative) ; the below ICSR fields/combinations of ICSR fields were reviewed and cases classified as following the second dose when one of the following condition was met:

- Mention of second dose in (free text field) 'Dosage text' [E2B(R2): B.4.k.6, E2B(R3): G.k.4.r.8]
- 2 distinct 'Drug(s) information' sections reporting Vaxzevria with 2 different administration dates [E2B(R2): B.4, E2B(R3): G]
- 2 distinct 'Dosage and Relevant Information' sections with Vaxzevria within the same drug section [E2B(R3): G.k.4]
- Vaxzevria was reported as 'Relevant past drug history' [E2B(R2): B.1.8, E2B (R3): D.8]
- COVID immunisation related terms were reported in 'Relevant medical history and concurrent conditions' [E2B(R2): B.1.7, E2B(R3): D.7]

However there is no assurance that all cases following the second dose were identified.

Analyses

The analyses used cases that occurred within 30 days of administration of the first and second dose and the person-time at risk for this same period. This time window was chosen as it covers the vast majority (>96%) of suspected cases of TTS occurring in the EEA reported to EV, and allows for a direct comparison with the incidence rates calculated in the interim report in April 2021. As reflected in the above data cut-off, a lag time of reporting to EV of seven days was assumed. Cases where the time of the occurrence of the event after vaccination was not reported were all considered to have occurred

[6] ECDC. Weekly surveillance report on COVID-19. Available from: https://www.ecdc.europa.eu/en/covid-19/surveillance/weekly-surveillance-report

within 30 days of the vaccination. Cases where the age was not reported were redistributed proportionally to the age categories.

Vaccination coverage data broken down by dose, age and sex was received from a majority of MSs and was extrapolated to the six remaining MSs.

The main analysis was conducted on the total EEA population to allow for comparison with the results from April, but also stratified by sex and by dose.

The robustness of the incidence rate estimates was assessed through sensitivity analyses, including:

(1) assuming under-reporting to EV using the same methodology followed in the previous exercise, i.e. as follows; 0% in the first seven days; 20% between day 8 and day 14; 50% after day 14. The level of underreporting is difficult to estimate;

(2) excluding six MSs for which no suitable stratified data could be obtained.

A standard methodology of measuring excess adverse events following vaccination is to measure the background rate of events and subtract this from the observed cases; the difference is assumed to be the excess, associated with vaccination. However, considering the distinct pattern of features of thrombosis associated with thrombocytopenia in people vaccinated with Vaxzevria, background incidence rates were not used in this analysis.

Analyses based on individual risks, including environmental, demographic and medical conditions that may impact TTS incidence rates, have not been performed.

Outcomes

TTS incidence rates in vaccinated per 100,000 person in 30 days after the first or second dose, stratified by age, were estimated either overall for the EEA, in males, in females, and are presented in the tables below for the main analysis, as well as the two sensitivity analyses.

Table 1. Main analysis: TTS Incidence rates in vaccinated per 100,000 persons in 30 days, after the first dose

First dose

	TTS cases			Person-time 30d - from ECDC			IR in vaccinated per 100,000 person in 30 days			
Age groups	Total	Male	Female	Total	Male	Female	April results	New results total	Male	Female
20-29	38	18	21	47,939,742	20,511,776	27,427,966	1.93	2.40	1.21	3.17
30-39	69	28	40	73,920,603	32,652,744	41,267,859	1.78	2.78	1.21	4.11
40-49	79	24	55	112,794,108	50,579,029	62,215,080	2.09	2.10	0.66	3.71
50-59	86	26	60	176,517,642	80,609,766	95,907,877	1.14	1.46	0.45	2.63
60-69	156	59	95	482,532,440	237,504,907	245,027,533	0.98	0.97	0.35	1.63
70-79	47	16	31	217,653,350	102,372,605	115,280,745	0.50	0.64	0.21	1.13
80+	15	5	9	36,665,801	16,678,082	19,987,719	0.45	1.19	0.44	1.96
Total	489	176	312	1,148,023,687	540,908,908	607,114,779	1.31	1.28	0.46	2.16

Table 2. Main analysis: TTS Incidence rates in vaccinated per 100,000 persons in 30 days, after the second dose

Second dose									
	TTS cases			Person-time 30d - from ECDC			IR in vaccinated per 100,000 person in 30 days		
Age groups	Total	Male	Female	Total	Male	Female	Total	Male	Female
20-29	0	0	0	20,663,730	7,992,105	12,671,625	0.00	0.00	0.00
30-39	1	1	0	34,807,840	14,509,693	20,298,147	0.10	0.10	0.00
40-49	2	1	1	53,353,676	22,292,411	31,061,265	0.12	0.06	0.16
50-59	0	0	0	83,100,573	36,379,194	46,721,379	0.00	0.00	0.00
60-69	4	1	4	168,982,099	82,159,541	86,822,558	0.08	0.02	0.17
70-79	2	1	1	119,876,885	56,672,486	63,204,399	0.06	0.02	0.08
80+	0	0	0	22,101,706	9,919,964	12,181,742	0.00	0.00	0.00
Total	10	4	6	502,886,510	229,925,395	272,961,115	0.06	0.02	0.09

Table 3. Sensitivity analysis assuming underreporting to EV: TTS Incidence rates in vaccinated per 100,000 persons in 30 days

Sensitivity analysis - underreporting									
	TTS cases			IR in vaccinated per 100,000 person in 30 days					
Age groups	Total	Male	Female	Main analysis total	under reporting total	Main analysis male	Under reporting male	Main analysis female	Under reporting female
20-29	48	21	27	2.40	2.98	1.21	1.46	3.17	4.07
30-39	90	37	54	2.78	3.64	1.21	1.57	4.11	5.46
40-49	100	30	71	2.10	2.67	0.66	0.82	3.71	4.82
50-59	113	36	78	1.46	1.92	0.45	0.63	2.63	3.41
60-69	212	87	125	0.97	1.32	0.35	0.51	1.63	2.15
70-79	62	20	42	0.64	0.85	0.21	0.28	1.13	1.54
80+	18	6	12	1.19	1.48	0.44	0.52	1.96	2.52
Total	643	237	409	1.28	1.68	0.46	0.61	2.16	2.83

Table 4. Sensitivity analysis without extrapolation of exposure data: TTS Incidence rates in vaccinated per 100,000 persons in 30 days, after the first dose

First dose - sensitivity analysis - excluding 6 member states										
	TTS cases		Person-time 30d - from ECDC		IR in vaccinated per 100,000 person in 30 days					
Age groups	Male	Female	Male	Female	Main analysis total	Excluding data total	Main analysis male	Excluding data male	Main analysis female	Excluding data female
20-29	5	11	14,070,342	18,814,601	2.40	1.43	1.21	0.52	3.17	2.35
30-39	9	31	22,398,611	28,308,271	2.78	2.35	1.21	0.58	4.11	4.53
40-49	16	29	34,695,399	42,677,313	2.10	1.75	0.66	0.63	3.71	2.90
50-59	18	41	55,295,407	65,789,363	1.46	1.45	0.45	0.45	2.63	2.62
60-69	44	65	162,919,846	168,080,097	0.97	1.00	0.35	0.37	1.63	1.63
70-79	14	22	70,223,934	79,078,456	0.64	0.72	0.21	0.27	1.13	1.17
80+	3	4	11,440,566	13,710,858	1.19	0.87	0.44	0.38	1.96	1.29
Total	108	203	371,044,105	416,458,958	1.28	1.19	0.46	0.41	2.16	2.05

Table 5. Sensitivity analysis without extrapolation of exposure data: TTS Incidence rates in vaccinated per 100,000 persons in 30 days, after the second dose

Second dose - sensitivity analysis - 6 member states										
	TTS cases		Person-time 30d - from ECDC		IR in vaccinated per 100,000 person in 30 days					
Age groups	Male	Female	Male	Female	Main analysis total	Excluding data total	Main analysis male	Excluding data male	Main analysis female	Excluding data female
20-29	0	0	6,186,400	8,692,280	0.00	0.00	0.00	0.00	0.00	0.00
30-39	0	0	11,231,429	13,923,801	0.10	0.00	0.10	0.00	0.00	0.00
40-49	0	2	17,255,750	21,306,913	0.12	0.10	0.06	0.00	0.16	0.30
50-59	0	0	28,159,820	32,049,190	0.00	0.00	0.00	0.00	0.00	0.00
60-69	0	2	63,596,733	59,557,160	0.08	0.03	0.02	0.00	0.17	0.11
70-79	1	0	43,868,124	43,355,950	0.06	0.04	0.02	0.03	0.08	0.00
80+	0	0	7,678,686	8,356,238	0.00	0.00	0.00	0.00	0.00	0.00
Total	1	3	177,976,941	187,241,533	0.06	0.03	0.02	0.01	0.09	0.07

In general, the following observations can be made:

- 30 day after the first dose:
    - the TTS incidence rates (1.28 per 100.000 first doses) are reasonably in line with the incidence rates estimated in April 2021 and reported in the interim report (1.31 per 100.000 first doses),
    - in adults aged 20 and older, TTS incidence rates decrease with increasing age, with the exception of the age range above 80 years old,
    - a higher risk of a TTS event in females compared to males is suggested across all age groups.
- A substantially lower TTS risk 30 days following the second dose compared to the TTS risk observed 30 days following the first dose is suggested (0.06 compared to 1.28 per 100.000 persons).
- The results of the sensitivity analysis, excluding the six countries that did not provide age and sex stratified data, are in line with the incidence rates of the total dataset.

2.3. Current evidence on the benefits and risks of the administration of a second dose of Vaxzevria

The second aspect which the Agency was asked to consider as part of this procedure in view of the risk of TTS, was to provide, if possible, a recommendation on the administration of the second dose of Vaxzevria, on the basis of available data.

As part of the assessment of this matter, the MAH was asked to provide the following information:

• Information on exposure to the second dose, stratified by 10-year age groups where available, for the EEA (per MS), for the UK and worldwide.

• Information on exposure to the second dose within phase 2/3 clinical trials (COV001, COV002, COV003, COV005, and D8110C00001), stratified by serologic status with:

- Two doses given 4 to 12 weeks apart

- Two doses given >12 weeks apart

• Results of a search of the AstraZeneca safety database and for adverse event reports of "embolic and thrombotic events" in association with the use of a second dose of Vaxzevria covering the period up to 15 July 2021.

• Results of a search of the EV database for adverse event reports of "embolic and thrombotic events" in association with the use of a second dose of Vaxzevria covering the period up to 28 June 2021.

• An overview of "embolic and thrombotic events" in ongoing and completed clinical trials.

• Available non-clinical and clinical safety and efficacy data of Vaxzevria following a single dose, after the first dose beyond 12 weeks, of the administration of a different COVID-19 vaccine as second dose, as well as a discussion thereof.

2.3.1. Number of second doses administered

In addition to the results of COV001, COV002, COV003 and COV005 study considered in the interim opinion, the results of the phase 3 trial D8110C00001 have become available since. In this clinical trial, 17,599 subjects seronegative at baseline and 521 subjects seropositive at baseline received a second dose of Vaxzevria with a 4-week interval. Median follow up time after the first dose was 92 days and 86 days for seronegative and seropositive subjects respectively. The median interval between the first and second dose was 29 days. Further, 5 subjects received the second dose with an interval longer than 12 weeks (median follow up time 121 days).

The cumulative number of second doses administered worldwide is not known. In the EEA, 23,440,976 persons have received a second dose of Vaxzevria. The majority were in the age bracket from 60 to 69 years. In the UK, 22,587,490 persons received a second dose. The majority were in the age bracket 50 to 59 years. The exposure to a second dose by age bracket for the EEA and UK is shown in Figure 1.

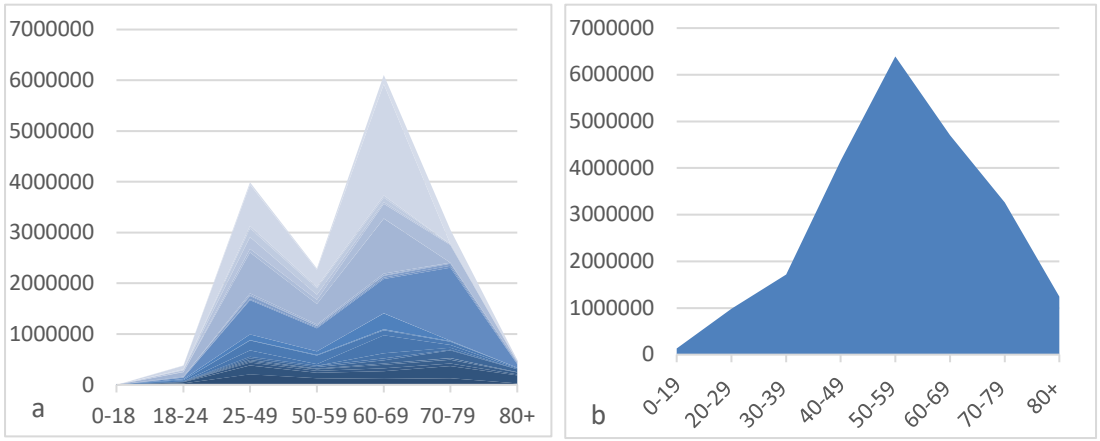

Figure 1. Exposure to a second dose of Vaxzevria in the EEA (a) and UK (b) per age band (different shades of blue in figure (a) correspond to different countries within the EEA)**.**

2.3.2. Available non-clinical data and clinical safety and efficacy data related to alternative scenarios for the second dose

Vaxzevria is intended to be given as two doses given 4 to 12 weeks apart, a recommendation which is supported by data submitted in support of the marketing authorisation application. An update of

available evidence and uncertainties for the administration of a second dose of Vaxzevria with an interval of 4 to 12 weeks after the first dose are summarised in Table 6.

Two alternative scenarios can be considered with regards to the administration of a second dose as follows:

1. Vaxzevria is given as a second dose but delayed,
2. No second dose is given,

Available evidence and uncertainties surrounding these scenarios are summarised in Table 7.

A third scenario was considered in the interim report in April, in which an mRNA vaccine is given as a second dose, following a single first dose of Vaxzevria. Preliminary results from non-commercial studies in Spain[7], Germany[8,9] and the UK[10] suggest a satisfactory immune response and no safety concerns, however further data is awaited and no definitive recommendation can be made at this stage[11] therefore this scenario is not included in Table 7.

Whilst it could also be considered to offer individuals who received a single dose of Vaxzevria a full two-dose mRNA vaccine regimen, the added benefit of restarting the vaccination course is questionable based on immunological principles. Uncertainties in this scenario would be comparable to the scenario in which a single mRNA dose is given, as a second dose. This possibility is not considered further in this assessment.

2.3.3. Thrombosis events with thrombocytopenia following administration of a second dose of Vaxzevria

Overall TTS cases reported in the EU/EEA

There have been no cases of TTS reported within the clinical trials conducted with Vaxzevria.

As mentioned in the COVID-19 vaccine safety update of Vaxzevria dated 14 July 2021, as of 27 June 2021, a total of 479 cases of suspected TTS with Vaxzevria were spontaneously reported to EV from EU/EEA countries; 100 of these reported a fatal outcome. These figures for suspected TTS refer to cases where events of thrombosis and thrombocytopenia were reported in combination; further case ascertainment is required to confirm TTS in these reported cases. About 51.4 million doses of Vaxzevria had been given to people in the EU/EEA by 20 June 2021[12].

TTS reporting rates post second dose internationally

As of 28 June 2021, using an estimated exposure of 38,854,532 people who had received Dose 2 of the AstraZeneca vaccine in the EU, UK, Philippines, and Australia, the reporting rate of thrombotic events in combination with thrombocytopenia following the second dose of Vaxzevria (with time to onset ≤ 21 days: 51 reports) was estimated to be 1.31 per million doses. The majority of reported TTS cases post second dose were in males (58.2%) and in older vaccinees (median age 69 years) than

[7] Borobia AM, Carcas AJ, Pérez Olmeda MT, et al. Reactogenicity and immunogenicity of BNT162b2 in subjects having received a first dose of ChAdOx1s: initial results of a randomised, adaptive, phase 2 trial (CombiVacS). Available at: https://ssrn.com/abstract=3854768 (accessed 21/06/21).
[8] Groß R, Zanoni M, Seidel A, et al. Heterologous ChAdOx1 nCoV-19 and BNT162b2 prime-boost vaccination elicits potent neutralizing antibody responses and T cell reactivity. Available at: https://www.medrxiv.org/content/10.1101/2021.05.30.21257971v1.full (accessed 21/06/21).
[9] Hillus D, Schwarz T, Tober-Lau P, et al. Safety, reactogenicity, and immunogenicity of homologous and heterologous prime-boost immunisation with ChAdOx1-nCoV19 and BNT162b2: a prospective cohort study. Available at: https://www.medrxiv.org/content/10.1101/2021.05.19.21257334v2 (accessed 21/06/21).
[10] Liu X, Shaw RH, Stuart ASV, et al. Safety and immunogenicity report from the Com-COV Study – a single-blind randomised non-inferiority trial comparing heterologous and homologous prime-boost schedules with an adenoviral vectored and mRNA COVID-19 vaccine. Available at: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3874014
[11] EMA and ECDC update on COVID-19 of 14 July 2021
[12] COVID-19 vaccine safety update for Vaxzevria (previously COVID-19 Vaccine AstraZeneca): 14 July 2021

those reported after the first dose. The rate of TTS following the second dose of the AstraZeneca vaccine is less than the background rate provided by the MAH (> 65 years) of 23.48[13] and 51.09[14]. However, considering the distinct pattern of features of thrombosis associated with thrombocytopenia in people vaccinated with Vaxzevria, the accuracy of these background rates is unclear. This rate of thrombotic events in combination with thrombocytopenia following the second dose of vaccine is below the estimated reporting rate of 13.89 per million doses for the first dose of Vaxzevria (961 identified reports with time to onset ≤ 21 days; estimated exposure 69,183,654 administered doses).

TTS cases post second dose in the EU/EEA

As of 15 July 2021, 89 cases of thrombosis in combination with thrombocytopenia following a second dose of Vaxzevria were identified in the MAH's safety database. Of these, n=53 (60%) occurred within 21 days of second dose. Case narratives were not provided for review and thus no further case ascertainment to confirm TTS in these reported cases was performed. Based on these numbers the reporting rate of TTS following the second dose of Vaxzevria is estimated to be 1.15 per million second doses (cases reported worldwide, exposure in EEA and UK only).

Most of the case reports (n = 62, 70%) occurred in vaccinees aged > 50 years, 52 (58%) of the 89 cases were in male vaccinees, and 36 (40%) in females. The time to onset ranged from less than 1 day to 46 days post second dose. Outcomes for the cases include recovered /recovering /recovered with sequelae in 41 cases, not recovered in 24 cases, fatal in 5 cases (6%), and unknown in 19 cases.

As of 18 July 2021, 10 cases of TTS following the second dose were identified in EV, with 6 in females (compared to 489 cases following the first dose of Vaxzevria, with 312 in females). Based on EEA exposure data the estimated incidence rate is 1.28 per 100,000 following the first dose and 0.06 per 100,000 following the second dose.

Of note, the UK MHRA reports 1.8 cases/million after second dose (0.9/million in 18-49y and 1.8/million >50y).[15]

[13] event rates per 1M PY per 21 days Truven Market Scan-2019, aligned with the OHDSI TTS algorithm
[14] event rates per 1M PY per 21 days Truven Market Scan-2019, aligned with the OHDSI TTS algorithm (with updated OHDSI-aligned codelists and washout periods)
[15] Coronavirus vaccine - weekly summary of Yellow Card reporting - updated 9 September 2021

Table 6. Available evidence for Vaxzevria given as a second dose with an interval of 4 to 12 weeks as recommended in the SmPC[16]

Second dose	Available Data Benefits	Available Data Risks	Uncertainties Benefits	Uncertainties Risks
Vaxzevria given at 4-12 weeks interval	Protection against symptomatic COVID-19 demonstrated for two doses given 4 to 12 weeks apart. In a pooled analysis of COV002 and COV003 the VE was estimated at 59.5% (95% CI: 45.8 – 69.7; 64/5,258 vs 154/5,210) In addition, in study D8110C00001, protection against symptomatic COVID-19 demonstrated for two standard doses 4 weeks apart was 74.0% (95% CI: 65.3 - 80.5; 73/17,662 vs 130/8,550). Protection has been demonstrated for 3 months after the second dose.	There is clinical trial data (COV001, COV002, COV003, COV005, D8110C00001) available in 56,623 persons of whom 33,869 received Vaxzevria (either 1 or 2 doses). Of these, 29,474 subjects received two doses at the recommended (standard) dose level. No cases of thrombosis combined with thrombocytopenia (TTS) have been reported in these trials. Post licensure, exposure to the second dose is known for the EEA (n=23,440,976) and UK (n=22,587,490). Eighty-nine cases of thrombosis + thrombocytopenia have been reported globally post dose 2 [AZ Global Patient Safety Database, cut off 15-07-2021], of which 53 had a TTO <21 days. Based on these numbers the reporting rate of TTS following the second dose of Vaxzevria is conservatively estimated to be 1.15 per million second doses[17].	Although protection has been demonstrated for 3 months after the second dose, it is likely to remain for longer. The exact period is not known at the moment.	The exposure to a second dose worldwide is not known. The actual interval between the two doses for post marketing exposure data is unknown. The follow up time after the second dose for the post marketing data is unknown. The exact incidence of TTS following vaccination with Vaxzevria is not known. Reports of TTS are based on spontaneous reporting, therefore likely to be an underestimation of cases occurring after vaccination.

[16] Data from clinical trials were obtained from the CHMP AR for variation II/02, based on DCO2 (7 December 2020) and the CMA, based on DCO1 (4 November 2020), as well as from variation II/26.
[17] Conservative estimate as this is based on globally reported cases and exposure only in the EEA/UK.

Table 7. Overview of current evidence of benefits and risks of alternative scenarios for completion of vaccination schedule[18]

Second dose	Available Data Benefits	Available Data Risks	Uncertainties Benefits	Uncertainties Risks
Vaxzevria given at >12 weeks	Protection against symptomatic COVID-19 demonstrated in 2,359 subjects who received the second dose with a >12-week interval; (8/1,146 in the Vaxzevria group vs 38/1,213 in the control group, VE: 77.6%, 95% CI:52.0 - 89.6). The second dose was administered up to 26 weeks after the first dose.	See Table 1. In clinical trials 1,146 (seronegative) persons received the second dose of Vaxzevria with an interval >12 weeks after the first dose, up to 26 weeks. There were no cases of TTS.	At the time of the marketing authorisation there was no evidence that the protection afforded by the first dose would extend beyond 12 weeks. Therefore, if the second dose is extended beyond this interval, vaccinees may be unprotected for a period of time before receiving the second dose.	See Table 1.
No second dose is given	Protection starts from approximately 3 weeks after 1st dose of vaccine and persists up to 12 weeks. The VE in participants who received at least one dose of the Vaxzevria vaccine was estimated at 50.5% (95% CI: 36.5 - 61.5)[19] against COVID-19 in studies COV002 and COV003, and at 54.5% (95%CI: 46.5 – 61.3) in study D8110C00001. In D8110C00001 efficacy between dose 1 and 2 was estimated at 53% (95%CI: 30 -68).	See Table 1. There are no additional risks other than lack of effect.	There is uncertainty around the level of protection afforded by a single dose of Vaxzevria; this could not be reliably estimated in the COV002 and COV003 trial. The estimate of protection afforded by a single dose in the D8110C000001 trial covers a 7-14-day period. It is not known whether the protection provided by the first dose lasts beyond the 12 weeks demonstrated in clinical trials.	None identified.

[18] Data from clinical trials were obtained from the CHMP AR for variation II/02, based on DCO2 (7 December 2020) and the CMA, based on DCO1 (4 November 2020), as well as from variation II/26.
[19] Data submitted in support of the CMA (DCO 4 November 2020: Any dose for Efficacy Analysis set, seronegative at baseline, participants who received at least one dose with follow up from the first dose).

3. Expert consultation

The CHMP sought the advice of the PRAC on the possibility to further characterise the risk of TTS further to vaccination with Vaxzevria based on the subset of the results of the study 'natural history of coagulopathy and use of anti-thrombotic agents in patients and persons vaccinated against SARS-COV-2' (EUPAS40414), titled 'thromboembolic events and thrombosis with thrombocytopenia after COVID-19 infection and vaccination in Catalonia (Spain) and the UK' (version 1.0, dated 29 June 2021), in particular with regards to possible risk factors, including sex.

Whilst further results are awaited from this study from Italy, France, Germany, the Netherlands and Spain (Madrid), data from those databases are not aimed at supporting further analyses related to the vaccines and will not include information on TTS after Vaxzevria.

Methods: Data sources are primary care computerised records from:

- Spain – SIDIAP (primary care records database of ~80% of the population of Catalonia) up till 26th May 2021. Cohorts included 426,272 Vaxzevria recipients and 4,570,149 general population participants.
- UK - CPRD GOLD/AURUM (GP records covering historical data on >20 million with active data for about 3.5 million participants) up till March 2021. Cohorts included 1,868,767 Vaxzevria (1 dose) vaccinees and 2,290,537 people from the general population.
- Sensitivity analyses were conducted focused on 1) people with at least one year of data visibility before index date; and 2) background rates focused on general population with at least one healthcare visit after 1/1/2017 (only for the UK analyses).

Outcomes of interest included venous thromboembolic events (VTE) (deep vein thrombosis (DVT), pulmonary embolism (PE), cranial vein thrombosis (CVT), visceral venous thrombosis) alone and in combination with concomitant thrombocytopenia (i.e. thrombosis-thrombocytopenia syndromes TTS), arterial thromboembolic events (ATE) (myocardial infarction or ischemic stroke), thrombocytopenia, and thrombosis-with-thrombocytopenia (TTS).

The co-occurrence of a thromboembolic event in combination with thrombocytopenia was used as definition for TTS. Co-occurrence was defined as thrombocytopenia identified/recorded within 10 days before/after the diagnosis of the thrombotic event.

Outcome rates were estimated for recipients of the Vaxzevria vaccine within 7, 14, 21, and 28 days after each dose where applicable.

Background rates were estimated in the general population for the period 2017-2019. Indirect standardisation was used to account for age-sex differences, and standardized incidence ratios (SIR) and [95% confidence intervals] reported for each cohort and outcome.

Results

Baseline characteristics

All vaccinated cohorts were older and had higher comorbidity and higher prevalence of use of many of the studied medicines than both the general population and COVID-19 ones.

Results from SIDIAP in Spain

Rare thrombosis (CVST, SVT, etc) and TTS events were too rare to stratify (< 5 events).

Results from CPRD in the UK

Co-occurrence of thromboembolic events and thrombocytopenia was very rare and the observed incidence rates of these events following vaccination with Vaxzevria were similar to those estimated in the background population. A summary of the 'observed versus expected' estimates is provided below.

Table 8. 'Observed versus expected' estimates related to thromboembolic events with thrombocytopenia in CPRD (UK) after vaccination with Vaxzevria

	N	Person-years	Observed events	Expected events	SIR (95% CI)
VTE with thrombocytopenia	1,868,547	119,132	7	6.4	1.09 (0.52 to 2.29)
ATE with thrombocytopenia	1,868,580	119,135	5	3.2	1.57 (0.65 to 3.78)
Stroke with thrombocytopenia	1,868,605	119,136	6	2.7	2.21 (0.99 to 4.91)

Note: The analyses of stroke with thrombocytopenia are based on sensitivity analyses.

Sensitivity analysis

- Findings were confirmed with sensitivity analysis (using first healthcare visit after 1/1/2017 vs a fixed index date of 1/1/2017 for background rate estimation and removing the requirement for a 1-year washout i.e. a first healthcare visit in 2017 for CPRD).
- Sensitivity analysis of stroke with concurrent thrombocytopenia indicated a higher than expected number of events in the Vaxzevria cohort with standardised incidence ratio (SIR) of 2.21 [0.99-4.91].

Key findings

- Rates of TTS were overall in line with expected rates.
- A sensitivity analysis of UK data showed a higher-than-expected rate of stroke with thrombocytopenia following ChAdOx1, equivalent to 3 excess cases in 1.9 million people.

Strengths and limitations

- This report contains the largest cohort study reported to date including data from two different European regions.
- Use of a common data model and sharing of analytical code to maximise the transparency and reproducibility of analyses.
- No access to hospital admissions data.
- People vaccinated in both participating countries were older and less healthy than the general population used to estimate background rates: analyses are limited by potential residual confounding by indication.

In addition to the limitations above noted by the authors, following points should be taken in consideration:

- It should be noted that further characterisation of the risk factors for TTS was not part of the research questions and objectives (in scope: estimation of incidence of TE events in vaccinated, comparison with background incidence).

- Only data from primary care was used: although the authors noted that previous studies have shown good correlation between primary care and hospital records in both databases, this is an important limitation for the characterisation of TTS events.
- The co-occurrence of thrombocytopenia identified/recorded within 10 days before/after the diagnosis of the thrombotic event was used as definition for TTS, and details on laboratory parameters e.g. anti-PF4 or D-dimer values were not available. It should be noted that the case-definition of TTS (or VITT) is still evolving (e.g. Brighton collaboration, MHRA, CDC, Haematology expert groups). The Expert Haematology Panel (EHP)[20] indicates that cases usually present 5-30 days after vaccination and are characterised by thrombocytopenia, raised D-Dimers and thrombosis, which is often rapidly progressive. They also recognise that deep vein thromboses (DVT) and pulmonary embolism can present up to 42 days after vaccination.
- The UK data lock point was mid-March, before TTS was recognised.
- In this study, TTS was very uncommon and no increase in risk was observed:
    - Further stratification by e.g. sex or other risk factors of these data will not bring additional evidence for further characterisation of risk as the power to demonstrate an increased risk in a stratum is too limited. Moreover, to demonstrate that the risk ratio is different in different strata, a test for interaction would be needed, this requires even more power.
    - Further adjustment for confounders will be difficult with the limited number of TTS events making it impossible to construct stable statistical models.
- Of note, a recent cohort study involving VITT patients (170 definite and 50 probable cases) in the UK found no sex preponderance and no identifiable medical risk factors[21].

Based on the available data, the PRAC considered that no new information could be identified to further characterise the risk of TTS following administration of Vaxzevria according to age groups or sex, or to identify risk factors.

4. Discussion

4.1. Risk characterisation

The CHMP supports the PRAC views that no relevant new information could be identified from the observational study (EUPAS40414) to further characterise the risk of TTS following the administration of Vaxzevria.

Spontaneous reports to EV were analysed using vaccination data from the MSs to characterise the risk of TTS, considering age and sex. The obtained incidence rates after the first dose of Vaxzevria are reasonably in line with the incidence rates estimated in April 2021 and reported in the interim opinion. The exact incidence of TTS following a first and second dose of Vaxzevria cannot be estimated based on available evidence, however the data suggests that TTS incidence rates 30 days after the first dose decrease with increasing age, apart from the age cohort 80 years and above, in which only few cases were observed resulting in highly uncertain estimates. A higher risk of a TTS event 30 days after the

[20] Guidance produced by the Expert Haematology Panel (EHP) focussed on Vaccine induced Thrombosis and Thrombocytopenia (VITT): https://b-s-h.org.uk/about-us/news/guidance-produced-by-the-expert-haematology-panel-ehp-focussed-on-vaccine-induced-thrombosis-and-thrombocytopenia-vitt/

[21] Pavord et al. Clinical Features of Vaccine-Induced Immune Thrombocytopenia and Thrombosis. NEJM, 2021. DOI: 10.1056/NEJMoa2109908

first dose in females compared to males is suggested. Furthermore, TTS rates 30 days following the second dose were substantially lower than the TTS rates observed 30 days following the first dose.

However, because of the type of data collection and corresponding limitations, these data cannot provide conclusive evidence and no strong conclusions should be made in terms of accurate predictive risk estimates.

Indeed, the TTS rates are based on spontaneous reports, as such they are subject to potential underreporting, and further reporting biases cannot be excluded. Whilst a sensitivity analysis taking into account potential underreporting has been conducted, it assumes a constant rate of underreporting across age groups and sexes which may not be realistic.

Further, suspected TTS cases were not subjected to individual case causality assessment, and assumptions have been made regarding TTS cases with missing age or missing time to onset. In addition, extrapolations have been made on the distribution of vaccination coverage data by dose, age and sex in a subset of MSs for which this data could not be obtained.

Specifically, regarding the risk after the second dose, the very low number of TTS events identified do not allow to make any relevant observations regarding age or sex distribution. Also, information in EV did not always allow to discriminate between events having occurred following a first or second dose in, thus there is no assurance that all cases following the second dose were identified and no firm conclusions on the level of risk of TTS or any risk factors following the second dose should be drawn.

Dose, age and sex stratified vaccination coverage data could not be obtained from six MSs, however excluding these MSs in a sensitivity analysis did not affect the conclusions. Nonetheless, the analysis was performed using pooled EEA data and it is known that there is heterogeneity[22] across the EU MSs. For example, country-specific data collection depends on the surveillance system at MS level, and these are not fully harmonised across the EU.

4.2. Administration of a second dose

Considering the data from spontaneously reported cases overall, there has been a shift in characteristics of reported cases of TTS following the second dose compared to the first. TTS cases reported following the second dose are in older persons who are more likely male compared to the cases of TTS following the first dose. TTS cases reported and calculated incidence rates following the second dose are substantially lower when compared with the first dose. This may reflect more restricted use of the vaccine, in particular of administration of the second dose, resulting from the identification of an increased risk of TTS, which was reported predominantly in younger individuals with initial reports mostly in women. As data are scarce and it is not always specified in case reports that cases occurred after the second dose, no firm conclusions should be drawn.

A scenario where no second dose is given could be considered under the assumption that this could avoid the additional risk of TTS after a second dose. However, whilst clinical studies demonstrated protection following the first dose, it was only demonstrated up to 12 weeks. There is, at present, insufficient data to inform the duration of protection after this period, and therefore, there can be no reassurance that individuals not given a second dose of any vaccine would maintain an adequate level of protection that would avoid an increase in COVID-19 cases. As the Delta variant increasingly spreads, the importance of completing the recommended two doses schedule of a two-dose vaccine to benefit from the highest level of protection against the virus was recently underlined[23].

[22] ECDC Managing heterogeneity when pooling data from different surveillance systems
[23] EMA and ECDC update on COVID-19 of 4 August 2021

There is no data to suggest that delaying the second dose may lower the risk of TTS. A recent publication of a study in 35 patients with TTS suggests waning of anti-PF4 antibodies within 12 weeks after vaccination[24], yet the role of vaccine induced anti-PF4 antibodies within the pathogenesis of TTS remains to be elucidated. Also, persons may be unprotected for a certain amount of time if the second dose is delayed beyond 12 weeks.

For subjects that will not receive a second dose of Vaxzevria, preliminary results from studies suggest a satisfactory immune response and no safety concerns with the administration of an mRNA vaccine for the second dose, however no definitive recommendations can be made at present in this regard[11].

5. Overall conclusion

Vaxzevria is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older. The overall benefits of Vaxzevria in the prevention of COVID-19 outweigh risks from adverse events including thrombosis in combination with thrombocytopenia (TTS).

The favourable effects of vaccination with Vaxzevria have been demonstrated in clinical trials. Vaccination has benefits in protecting against COVID-19 and observational studies suggest that it reduces the risk of hospitalisation from COVID-19.

Vaxzevria has been associated with an increased risk of TTS. The frequency of those events has been characterised as very rare based on current reporting rates. TTS requires rapid identification and urgent clinical management. Guidance on the management of suspected TTS has been provided by learned societies[25]. No risk factors were identified for TTS at time of start of this review.

In April 2021, to support decision making relating to vaccination campaigns at national level, the CHMP performed further analyses assuming different levels of effectiveness of the vaccine and different levels of TTS risk and stratifications of the data by age groups. The analyses showed that the benefits of vaccination increase with increasing age and increasing infections rates, however the data available did not allow to stratify the analyses by sex, nor to identify other possible risk factors. Conclusions from this analysis remain valid.

Results of a new observational study collecting data on TTS from primary care records did not provide new information to further characterise the risk of TTS following administration of Vaxzevria according to age groups or sex, or to identify risk factors.

Data on TTS from spontaneous reporting, including in EudraVigilance, also when put in the context of exposure data by age group and by sex in EEA Member States, allow to make a number of observations, however the CHMP was of the view that no strong conclusions should be drawn in terms of accurate predictive risk estimates.

With regards to a possible recommendation on the administration of the second dose, the CHMP considered available data on the occurrence of TTS following the second dose as well as safety and efficacy aspects of different scenarios surrounding the second dose.

The CHMP concluded that two separate doses of Vaxzevria should be administered 4 to 12 weeks apart, in line with the current product information. The mechanism behind the observed cases of TTS remains unclear, and whilst spontaneous reporting suggests that the risk following the second dose may be lower than the risk observed following the first dose, no firm conclusion should be drawn.

[24] Schönborn L, Thiele T, Kaderali L, Greinacher A. Decline in Pathogenic Antibodies over Time in VITT. N Engl J Med. 2021 Sep 8.
[25] EMA raises awareness of clinical care recommendations to manage suspected thrombosis with thrombocytopenia syndrome

Appendix 1 - April 2021 analyses from report EMA/CHMP/214855/2021

Risk contextualisation

The first aspect which the Agency was asked to consider was to contextualise the reports of TTS with the benefits of the vaccination by age and/or sex, as well as to identify possible additional risk factors for the occurrence of the TTS reactions.

Measures

Based on public health relevance and availability of data as of 21 April 2021, the following parameters were used.

Potential benefits

Potential benefits of vaccination with Vaxzevria were described for the following three outcomes:

1) COVID-19 related hospitalisations prevented
2) COVID-19 related intensive care unit (ICU) admissions prevented
3) COVID-19 related deaths prevented

As potential benefits depend on the level of exposure to the circulating virus and individual characteristics (i.e. age) this analysis takes into consideration the following factors:

- Age categories: 20-29; 30-39; 40-49; 50-59; 60-69; 70-79; ≥ 80
- Background SARS-CoV2 virus exposure, divided into three categories, using overall COVID-19 incidence as submitted by MSs:
    - "Low" exposure: using virus circulation for September 2020 (incidence: 55/100,000 population)
    - "Medium" exposure: using virus circulation for March 2021 (incidence 401/100,000 population)
    - "High" exposure: using virus circulation for January 2021 (incidence 886/100,000 population)

Analyses are at a population level. Analyses based on individual risks, including occupation and other medical conditions that might increase exposure or the seriousness of the infection, have not been analysed. Neither has the analysis taken into account reduced vaccine efficacy against SARS CoV-2 variants.

Potential harms

Potential harms were assessed based on the number of spontaneously reported cases in EudraVigilance of TTS in patients having received Vaxzevria.

Methods and analysis

Calculation

COVID-19 related events prevented per 100,000 vaccinated patients over a four-month and three-month period were estimated by applying Vaxzevria effectiveness data and the background incidence of virus exposure to the number of COVID-19 related hospitalisation, ICU admission and death events.

Within each age strata, the following calculation was used:

$$events\ prevented \begin{bmatrix} hospitalised \\ ICU\ admitted \\ deaths \end{bmatrix} = COVID\ incidence\ rate \times proportion\ with\ event \times vaccine\ effectiveness$$

Potential harms were defined as TTS cases in persons exposed to Vaxzevria per 100,000 per month as reported to EudraVigilance:

$$potential\ harms = \frac{observed\ events\ (EudraVigilance)}{persons\ exposed\ to\ AZ\ vaccine}$$ [26]

Data sources

Data sources included data on COVID-19 infection and vaccination from the MS obtained either directly or through European Centre for Disease Prevention and Control (ECDC)[27], the literature, and EudraVigilance.

Potential benefits

EEA MS were asked to submit the below information by age group (0-19; 20-29; 30-39; 40-49; 50-59; 60-69; 70-79; ≥80) by sex (F/M/Unknown) for their respective MS. The same information was requested from ECDC. The request included:

- The number of vaccinated persons with Vaxzevria by week up to the most recent date stratified by dose (1st and 2nd)
- Number of COVID-19 infection, hospitalisations, ICU admissions, and deaths by month from January 2021 to March 2021
- Population size by month

Incidence rates of COVID-19 infection were received from the ECDC[28] and directly from Member States and these were broken down by age categories (20-29; 30-39; 40-49; 50-59; 60-69; 70-79; ≥80).

[26] Clarification on 16 September 2021: "persons exposed to AZ vaccine" is calculated in person time at risk during 30 days following the administration of a dose of Vaxzevria. The ratio obtained is then multiplied by 100,000 and 30 to obtain the incidence rate per 100,000 per month/30 day

[27] Data from The European Surveillance System – TESSy, provided by Austria, Croatia, Czech Republic, Denmark, Finland, Germany, Ireland, Italy, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Slovakia, Sweden and released by ECDC. The views and opinions of the authors expressed herein do not necessarily state or reflect those of ECDC. The accuracy of the authors' statistical analysis and the findings they report are not the responsibility of ECDC. ECDC is not responsible for conclusions or opinions drawn from the data provided. ECDC is not responsible for the correctness of the data and for data management, data merging and data collation after provision of the data. ECDC shall not be held liable for improper or incorrect use of the data.

[28] ECDC. Weekly surveillance report on COVID-19. Available from: https://www.ecdc.europa.eu/en/covid-19/surveillance/weekly-surveillance-report (accessed 16-Apr-2021)

Age distributions were extrapolated to those countries that did not report data according to requested age categories.

The proportions of hospitalisations, ICU admissions and deaths following COVID-19 infection across EAA MS were estimated from across EEA MSs, based on a subset of EEA MS as provided by ECDC and collected from the MSs. The data from the two sources were compared for validation.

Data broken down by sex was received from a subset of MS, but were insufficient to allow validation of extrapolation to all EEA MS. Therefore, no stratification by sex could be performed.

No further stratification on other risk factors for severe COVID disease, including underlying health condition or obesity, was performed as relevant data were not available.

The proportion of prevented hospitalisations is assumed to be the same as the proportion of prevented ICU admissions and deaths. Health policy measures in the recent months may have led to different exposures of populations across MS over months, and this may have led to different risks.

Data sources for efficacy and risk (TTS) are described under the contextualisation section (Section 2.2.3)

Contextualisation: analyses and additional sensitivity analyses

To contextualise the robustness of effect estimates of the effectiveness of Vaxzevria and the occurrence of TTS, several approaches were developed with different assumptions regarding efficacy level, benefit window and potential harms. Analyses relate to average benefits and risks for individuals.

Efficacy level

Vaxzevria effectiveness (VE) is estimated using different data sources and assumptions.

- Firstly, effectiveness is derived from observational studies. Two studies in the public domain have results on VE against hospitalisation.[29,30] VE increased with time in the month following the first dose to 80% overall. A constant vaccine effectiveness from these observational studies of 85% in the 18-64 years of age, 79% in the 65-79 years of age and 81% in those above 80 years of age was used. This approach is seen as the best-case scenario.
- Secondly, from observational studies and based on the available knowledge from clinical trials and the literature, effectiveness levels of the Vaxzevria after 1st dose are increasing over the first weeks following administration of the first dose. The second analysis was performed assuming no effectiveness of 1st dose of Vaxzevria for the first three weeks and after the third week a constant effectiveness of 18-59yrs=85%;60-79yrs=79%; ≥80=81% based on the two observational studies.
- Thirdly, effectiveness is extrapolated from clinical trials at 60% for symptomatic COVID-19 infection.[31] It is noted this might be a conservative estimate given that pooled VE in the time period starting 21 days after dose 1 until dose 2 (censored at 12 weeks post dose 1) in subjects who received standard dose for each doses (SD/SD) is estimated at 73.2% (95% CI: 54.3, 84.3). Effectiveness at 60% is therefore seen as a conservative scenario.

[29] Vasileiou, Eleftheria and Simpson, 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: http://dx.doi.org/10.2139/ssrn.3789264
[30] Jamie Lopez Bernal, Nick Andrews, Charlotte Gower, 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: https://doi.org/10.1101/2021.03.01.21252652
[31] Assessment report COVID-19 Vaccine AstraZeneca EMA/94907/2021

Benefits window

Benefit parameters were estimated as prevented cases per 100,000 occurring in a four-month and a three-month window. While data for benefits in a three-month window are more comprehensive, in clinical practice, a four-month benefit window is considered a less conservative scenario based on demonstrated persistence of immune response beyond the three months. A proportion of subjects in the pivotal clinical trials were administered the second dose of the vaccine beyond three months of the first dose. Although there is no direct evidence that the protection afforded by the first dose would extend beyond 12 weeks, based on antibody kinetics and Kaplan Meier (KM) curves for efficacy a sharp drop in level of antibodies past that time is considered unlikely, and therefore protection can be assumed to reasonably persist over the first 4 months, or longer, but sufficient data are yet lacking.

Potential harms

The number of TTS cases in patients exposed to Vaxzevria is extracted from EudraVigilance, the European database of reports of suspected adverse drug reactions. The analysis uses cases that occur within 1-month of vaccination. This time window was chosen as it covers all cases of TTS occurring in the EEA in EudraVigilance. Therefore, extending the time window beyond 30 days has currently no impact on the analysis. There were 16 cases where the time of the occurrence of the event after vaccination was not reported; these were all considered likely to have occurred within 1-month of the vaccination.

A search was therefore performed in EudraVigilance (data cut off: 13 April 2021) with the MedDRA SMQ 'Embolic and thrombotic events' and specific preferred terms (PT: acquired amegakaryocytic thrombocytopenia, anti-platelet antibody, autoimmune heparin-induced thrombocytopenia, heparin-induced, thrombocytopenia, heparin-induced thrombocytopenia test, heparin-induced thrombocytopenia test positive, immune thrombocytopenia, megakaryocytes abnormal, megakaryocytes decreased, non-immune heparin associated thrombocytopenia, platelet aggregation abnormal, platelet anisocytosis, platelet count, platelet count abnormal, platelet count decreased, platelet disorder, platelet maturation arrest, platelet production decreased, platelet toxicity, plateletcrit abnormal, plateletcrit decreased, spontaneous heparin-induced thrombocytopenia syndrome, thrombocytopenia, thrombocytopenia neonatal, thrombocytopenic purpura, thrombotic thrombocytopenic purpura) with COVID-19 VACCINE ASTRAZENECA (CHADOX1 NCOV-19), to identify all cases of TTS. Therefore, cases were identified based on structured reporting, and were not subjected to individual case causality assessment.

A total of 142 cases were identified in EudraVigilance.

Background rates of TTS

TTS associated with vaccination with Vaxzevria is usually associated with anti-PF4 antibodies, and thromboses are found in large vessels at unusual locations including cerebral veins and splanchnic vessels. This represents a distinct pattern of features compared to thrombosis associated with thrombocytopenia in the background population; thus no measurable background incidence is assumed.

A standard methodology of measuring excess adverse events following vaccination is to measure the background rate of events and subtract this from the observed cases; the difference is assumed to be the excess, associated with vaccination. However, considering the distinct pattern of features of thrombosis associated with thrombocytopenia in people vaccinated with Vaxzevria, background incidence rates were not used in the analysis and the harms are estimated by considering only the cases observed in EudraVigilance without any adjustment for expected background rates.

Under reporting to EudraVigilance

For the analysis of harm, the number of TTS cases was taken as reported from the EEA in EV. Because of the established under-reporting seen in spontaneous reporting systems, a second (sensitivity) analysis was made assuming an under-reporting of TTS cases reported to EV. For this analysis an underreporting of TTS cases to EV was assumed as follows; 0% in the first seven days; 20% between day 8 and day 14; 50% after day 14 (Lévy, 2002; Prevots, 1994)[32,33]. The level of underreporting is difficult to estimate.

Outcomes

The outcomes for the different analyses under the different scenarios are provided [at the end of this document]. Table 1 provides the numbers assessing potential benefits over a four-month period, and Table 22 provides the numbers assessing potential benefits over a three-month period. It should be noted that all estimates are accompanied by uncertainties, both based on estimation uncertainty and based on the limitations of the data discussed above.

This exercise has put the very rare cases of TTS in the context of the benefits of vaccination. The analyses conducted show that the benefits of vaccination increase with increasing age and increasing infections rates. Details on different scenarios of age and infection rate for hospitalisation, ICU admission and death, together with TTS risk are presented in this assessment report based on different assumptions of vaccine effectiveness and risk.

While the COVID-19 events prevented and the TTS cases (risks) are presented in detail in the [tables below], it is illustrative to make observations based on a reasonable set of assumptions.

If one considers the analysis using 80% effectiveness (the best-case scenario) over a four-month window compared to the unadjusted TTS cases, the following observations can be made:

- Hospital admissions prevented are numerically higher than TTS cases across all age categories, and all virus exposure levels;
- ICU admissions prevented are numerically higher than TTS cases across all age categories for medium and high virus exposures and above 60 years at low virus exposure and;
- Deaths prevented are numerically higher than TTS cases in those above 30 years for high and medium virus exposures; and above 60 years for low virus exposure.

If one considers the analysis using 60% effectiveness (the conservative scenario) over a four-month window (effectiveness assumed to start from three weeks onwards) compared to the unadjusted TTS cases, the following observations can be made:

- Hospital admissions prevented are numerically higher than TTS cases across all age categories, and all virus exposure levels;
- ICU admissions prevented are numerically higher than TTS cases across all age categories for medium and high virus exposures and above 60 years at low virus;
- Deaths prevented are numerically higher than TTS cases in those above 30 years for high virus exposure; above 40 years for medium virus exposure and above 60 years for low virus exposure.

[32] Lévy-Bruhl D, Desenclos JC, Rebière I, Drucker J. Central demyelinating disorders and hepatitis B vaccination: a risk-benefit approach for pre-adolescent vaccination in France. Vaccine 2002; 20: 2065-2071.
[33] Prevots R, Sutter R, Strebel P, et al. Completeness of reporting for paralytic poliomyelitis, United States, 1980 through 1991: implications for estimating the risk of vaccine-associated disease. Arch Pediatr Adolesc Med 1994; 148: 479-485.

The analyses detailed are based on the data currently available. Assumption and extrapolation have been made that need to be considered when interpreting the results.

Analyses are at a population level. Analyses based on individual risks including occupation and other medical conditions that might increase exposure or the seriousness of infection, have not been performed.

Additional discussion and limitations

The outcomes presented in this analysis provide an EEA contextualisation of the harms of Vaxzevria using major clinical events prevented by vaccination using different assumptions. In addition to the assumptions and sensitivity analyses described above, additional assumptions and limitations should be taken into consideration.

Parameters used for this analysis are estimated on the data available to the EMA at the time of the analysis. While age-specific data have been obtained from the majority of MSs, it has been assumed that the age specific distribution is representative for MSs from which data were not obtained. Sex-specific data was obtained from a small subset of MS, which did not allow to a validated an extrapolation to the remaining MS, and this was not further pursued. The proportion of patients hospitalised, with ICU admission and death following COVID-19 infection was estimated on a subset of EEA MS as provided by ECDC and collected from the MS and was considered representative of the whole EEA.

It is known that there is heterogeneity[34] across the EU MSs. For example, country specific values depend on the vaccination policies and strategies at MS level and these are not fully harmonised. In addition, the circulation of the virus differs in both temporal and geographical terms in Europe. As MSs only reported data from 2021 onwards, the COVID-19 incidence rate for the low exposure scenario (virus circulation in September 2020) was estimated based on the case-based data submitted to ECDC by MSs).

An alternative approach to assessing the benefits of vaccination was tested as a sensitivity analysis: this simply multiplied the vaccine effectiveness by the incidence rate for each outcome derived from ECDC / MS data. This was found to have little impact on the estimated vaccine benefits. Additionally, this approach did not fully allow contextualisation with a "low" background COVID-19 incidence because event-specific background data are only available for the past three months. As a result, this alternative approach is not included in the assessment report.

The effectiveness data for Vaxzevria was derived from two observational studies and complemented with two additional analyses, one based on varying effectiveness over time and one based on the clinical trial estimate of efficacy for symptomatic disease. Evidence from observational studies can be questioned based on potential confounders (notably the impact of social distancing measures imposed in temporal association with vaccination roll-out). On the other hand, the external validity of clinical trials efficacy can be considered as valid and results thereof have been considered in parts of the scenarios.

It should be noted that equal effectiveness is assumed across all three benefit parameters.

The lag-time between vaccination of individuals, TTO and then reporting to EudraVigilance as well as the impossibility to investigate the platelet count in the event of sudden death due to multiple thromboses and bleedings, may have led to a few fatalities not having been considered, with a

[34] ECDC Managing heterogeneity when pooling data from different surveillance systems

consequence of some underestimation in cases. Certainty around this will improve with more data becoming available.

Overall discussion and conclusion

Vaxzevria is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older. The overall benefits of Vaxzevria in the prevention of COVID-19 outweigh risks from adverse events including thrombosis in combination with thrombocytopenia (TTS).

The favourable effects of vaccination with Vaxzevria have been demonstrated in clinical trials. Vaccination has benefits in protecting against COVID-19 and observational studies suggest that it reduces the risk of hospitalisation from COVID-19.

Vaxzevria has been associated with an increased risk of TTS. The frequency of those events has been characterised as very rare based on current reporting rates. No risk factors have been identified for TTS at present.

To support decision making relating to vaccination campaigns at national level, the reports of TTS are presented in the context of the benefits of vaccination stratified by age and considering the background infection rate. The analysis does not take into consideration individual risk of infection, e.g. occupation or risk of severe COVID-19 based on comorbidities. When conducting this analysis, the benefits of the vaccine were described using data from the marketing authorisation dossier of Vaxzevria, published studies, data provided by the Member States and ECDC and were estimated in terms of:

- COVID-19 related hospitalisations prevented
- COVID-19 related ICU admissions prevented
- COVID-19 related deaths prevented

In this analysis, it was not possible to further stratify risk by sex, as data on sex was received from only a subset of Member States and it was not possible to validate extrapolation to the remaining Member States.

Benefits were expressed as a function of age and level of viral circulation. The risk of TTS was estimated based on a number of spontaneously reported cases in EudraVigilance in patients having received Vaxzevria and the exposure data for Vaxzevria.

In order to reflect the different situations in the different MSs and changing situation over time and understanding that different parameters may be important for decision making, different scenarios have been assessed, which gave different estimates of benefits and risks. Infection rate and hospitalisation, ICU and death are used to contextualise the occurrence of TTS.

Different assumptions on estimates on the level of benefit and level of risk have been made:

- several assumptions on the level and duration of protection provided by the vaccine;

- two assumptions for risk using the absolute number of cases of TTS reported to EudraVigilance and adjusting this number based on presumed underreporting.

In addition, the circulation of the virus differs in both temporal and geographical terms in Europe. As Member States only reported data from 2021 onwards, the COVID-19 incidence rate for the low exposure scenario (virus circulation in September 2020) was calculated based on the case-based data from the ECDC (drawn from 9 Member States).

This exercise has put the very rare cases of TTS in the context of the benefits of vaccination. The analyses conducted show that the benefits of vaccination increase with increasing age and increasing infections rates. Details on different scenarios of age and infection rate for hospitalisation, ICU admission and death, together with TTS risk are presented in the assessment report based on different assumptions of vaccine effectiveness and risk.

For example, if one considers the analysis using 80% effectiveness (the best-case scenario) over a four-month window compared to the unadjusted TTS cases, the following observations can be made:

- Hospital admissions prevented are numerically higher than TTS cases across all age categories and all virus exposure levels;
- ICU admissions prevented are numerically higher than TTS cases across all age categories for medium and high virus exposures and above 60 years at low virus exposure and;
- Deaths prevented are numerically higher than TTS cases in those above 30 years for high and medium virus exposures; and above 60 years for low virus exposure.

If one considers the analysis using 60% effectiveness (the conservative scenario) over a four-month window (effectiveness assumed to start from three weeks onwards) compared to the unadjusted TTS cases, the following observations can made:

- Hospital admissions prevented are numerically higher than TTS cases across all age categories and all virus exposure levels;
- ICU admissions prevented are numerically higher than TTS cases across all age categories for medium and high virus exposures and above 60 years at low virus;
- Deaths prevented are numerically higher than TTS cases in those above 30 years for high virus exposure; above 40 years for medium virus exposure and above 60 years for low virus exposure.

The analyses are based on the data currently available. Assumption and extrapolation have been made that need to be considered when interpreting the results.

These are only interim results and may be subject to change as more is known about the risk of TTS and the favourable effects of vaccination with Vaxzevria. However, these results based on the agreed methodology can be used to help guide vaccination decisions at national level including on optimal use of Vaxzevria as part of the armamentarium.

To better support this contextualisation exercise, key aspects of this analysis have been presented graphically.

Visual risk contextualisation EMA/234525/2021

Table 1. Model outcomes assessing COVID-19 related hospitalisation, ICU admission and deaths per 100,000 over four months

Overview of the outputs of the models under different scenario's (prevented benefits calculated per 100,000 over four months)																						
						Model 1	Model 2	Model 3			Model 1	Model 2	Model 3					Model 1	Model 2	Model 3	Model 4	Model 5	
Age categories	Total number vaccinated with AZ	COVID-19 incidence per/100,000 per month	COVID-19 incidence per/100,000 per four months	Hosp rate (%)	COVID-19 hospitalisation per/100,000 per four months	COVID-19 prevented hospitalisation/100,000 per four months	COVID-19 prevented hospitalisation/100,000 per four months	COVID-19 prevented hospitalisation/100,000 per four months	ICU rate (%)	COVID-19 ICU admission per/100,000 per four months	COVID-19 prevented ICU admission/100,000 per four months	COVID-19 prevented ICU admission/100,000 per four months	COVID-19 prevented ICU admission/100,000 per four months	Death rate (%)	COVID-19 death per/100,000 per four months	COVID-19 prevented death/100,000 per four months	COVID-19 prevented death/100,000 per four months	COVID-19 prevented death/100,000 per four months	Cases of TTS after 1st dose/100,000	Cases of TTS after 1st dose/100,000	Fatal TTS cases afster 1st dose of those that reported deaths status (41% of 142 cases)/100,000
Medium circulation of the virus																						
20-29	1269332	597	2389	1.8%	43	37	30	21	0%	4	3	3	2	0%	0	0	0	0	1.9	2.7	**0.1**
30-39	1922817	586	2342	2.7%	63	54	44	31	0%	6	5	4	3	0%	2	2	2	1	1.8	2.1	**0.5**
40-49	2796826	643	2571	3.7%	95	81	66	46	0%	12	10	8	6	0%	8	7	5	4	2.1	2.7	**0.9**
50-59	3256014	501	2003	6.7%	134	114	92	65	1%	18	15	12	9	0%	9	8	6	4	1.1	1.4	**0.2**
60-69	5081118	403	1610	14.3%	231	183	148	113	2%	36	28	23	17	2%	32	25	21	16	1.0	1.3	**0.3**
70-79	3122185	307	1228	28.6%	352	278	225	171	4%	50	39	32	24	9%	111	87	71	54	0.5	0.9	**0.2**
80+	786448	289	1156	35.5%	410	332	267	200	3%	36	29	24	18	21%	243	197	158	118	0.4	0.4	**0.2**
TOTAL						1077	871	647			131	106	79			326	262	197			
Low circulation of the virus																					
20-29	1269332	66	264	1.8%	5	4	3	2	0%	0	0	0	0	0%	0	0	0	0	1.9	2.7	**0.1**
30-39	1922817	52	207	2.7%	6	5	4	3	0%	1	0	0	0	0%	0	0	0	0	1.8	2.1	**0.5**
40-49	2796826	51	205	3.7%	8	6	5	4	0%	1	1	1	0	0%	1	1	0	0	2.1	2.7	**0.9**
50-59	3256014	46	182	6.7%	12	10	8	6	1%	2	1	1	1	0%	1	1	1	0	1.1	1.4	**0.2**
60-69	5081118	42	167	14.3%	24	19	15	12	2%	4	3	2	2	2%	3	3	2	2	1.0	1.3	**0.3**
70-79	3122185	50	201	28.6%	57	45	37	28	4%	8	6	5	4	9%	18	14	12	9	0.5	0.9	**0.2**
80+	786448	132	526	35.5%	187	151	121	91	3%	17	13	11	8	21%	110	90	72	54	0.4	0.4	**0.2**
TOTAL						241	194	145			26	21	16			108	87	65			
High circulation of the virus																					
20-29	1269332	1051	4205	1.8%	76	64	52	37	0%	7	6	5	3	0%	0	0	0	0	1.9	2.7	**0.1**
30-39	1922817	888	3551	2.7%	96	81	66	47	0%	9	8	6	5	0%	4	3	2	2	1.8	2.1	**0.5**
40-49	2796826	969	3877	3.7%	143	122	99	70	0%	18	15	12	9	0%	12	10	8	6	2.1	2.7	**0.9**
50-59	3256014	917	3667	6.7%	245	208	169	119	1%	33	28	23	16	0%	17	14	11	8	1.1	1.4	**0.2**
60-69	5081118	715	2860	14.3%	410	324	263	200	2%	64	50	41	31	2%	57	45	37	28	1.0	1.3	**0.3**
70-79	3122185	605	2421	28.6%	693	547	443	337	4%	98	78	63	48	9%	218	172	139	106	0.5	0.9	**0.2**
80+	786448	1077	4310	35.5%	1530	1239	994	745	3%	135	110	88	66	21%	905	733	588	441	0.4	0.4	**0.2**
TOTAL						2587	2087	1555			295	238	177			977	786	590			

*** Explanation of the models**

Model 1: Effectiveness Vaxzevria (18-64 years of age=85%;65-79 years of age= 79%;>80 years of age=81% (Bernal et al., Vasileiou et al.))
Model 2: Effectiveness Vaxzevria is assumed to start from three weeks onwards (18-64 years of age=85%;65-79 years of age=79%;>80 years of age=81%)
Model 3: Effectiveness Vaxzevria is assumed to start from three weeks onwards (60% effectiveness (pre-licensing trial))
Model 4: No underreporting of TTS cases to EudraVigilance
Model 5: Sensitivity analysis for underreporting of TTS cases to EudraVigilance (0% first 7 days; 20% between day 8 and day 14; 50% after day 14)

Table 2. Model outcomes assessing COVID-19 related hospitalisation, ICU admission and deaths per 100,000 over three months

Overview of the outputs of the models under different scenario's (prevented benefits calculated per 100,000 over three months)																					
						Model 1*	Model 2	Model 3			Model 1	Model 2	Model 3				Model 1	Model 2	Model 3	Model 4	Model 5	
Age categories	Total number vaccinated with AZ	COVID-19 incidence per/100,000 per month	COVID-19 incidence per/100,000 per three months	Hosp rate (%)	COVID-19 hospitalisation per/100,000 per three months	COVID-19 prevented hospitalisation/100,000 per three months	COVID-19 prevented hospitalisation/100,000 per three months	COVID-19 prevented hospitalisation/100,000 per three months	ICU rate (%)	COVID-19 ICU admission per/100,000 per three months	COVID-19 prevented ICU admission/100,000 per three months	COVID-19 prevented ICU admission/100,000 per three months	COVID-19 prevented ICU admission/100,000 per three months	Death rate (%)	COVID-19 death per/100,000 per three months	COVID-19 prevented death/100,000 per three months	COVID-19 prevented death/100,000 per three months	COVID-19 prevented death/100,000 per three months	Cases of TTS after 1st dose/100,000	Cases of TTS after 1st dose/100,000	Fatal TTS cases afster 1st dose of those that reported deaths status (41% of 142 cases)/100,000
Medium circulation of the virus																					
20-29	1269332	597	1792	1.8%	32	27	19	15	0%	3	3	2	1	0%	0	0	0	0	1.9	2.7	**0.1**
30-39	1922817	586	1757	2.7%	47	40	28	21	0%	5	4	3	2	0%	2	1	1	1	1.8	2.1	**0.5**
40-49	2796826	643	1928	3.7%	71	61	43	32	0%	9	7	5	4	0%	6	5	3	3	2.1	2.7	**0.9**
50-59	3256014	501	1502	6.7%	100	85	60	45	1%	14	11	8	6	0%	7	6	4	3	1.1	1.4	**0.2**
60-69	5081118	403	1208	14.3%	173	137	104	78	2%	27	21	16	12	2%	24	19	14	11	1.0	1.3	**0.3**
70-79	3122185	307	921	28.6%	264	208	158	119	4%	37	30	22	17	9%	83	65	50	37	0.5	0.9	**0.2**
80+	786448	289	867	35.5%	308	249	185	138	3%	27	22	16	12	21%	182	147	109	82	0.4	0.4	**0.2**
TOTAL						808	598	448			98	73	55			244	182	137			
Low circulation of the virus																					
20-29	1269332	66	198	1.8%	4	3	2	2	0%	0	0	0	0	0%	0	0	0	0	1.9	2.7	**0.1**
30-39	1922817	52	155	2.7%	4	4	3	2	0%	0	0	0	0	0%	0	0	0	0	1.8	2.1	**0.5**
40-49	2796826	51	153	3.7%	6	5	3	3	0%	1	1	0	0	0%	0	0	0	0	2.1	2.7	**0.9**
50-59	3256014	46	137	6.7%	9	8	5	4	1%	1	1	1	1	0%	1	1	0	0	1.1	1.4	**0.2**
60-69	5081118	42	125	14.3%	18	14	11	8	2%	3	2	2	1	2%	2	2	1	1	1.0	1.3	**0.3**
70-79	3122185	50	150	28.6%	43	34	26	19	4%	6	5	4	3	9%	14	11	8	6	0.5	0.9	**0.2**
80+	786448	132	395	35.5%	140	113	84	63	3%	12	10	7	6	21%	83	67	50	37	0.4	0.4	**0.2**
TOTAL						181	134	101			19	14	11			81	60	45			
High circulation of the virus																					
20-29	1269332	1051	3153	1.8%	57	48	34	26	0%	5	5	3	2	0%	0	0	0	0	1.9	2.7	**0.1**
30-39	1922817	888	2663	2.7%	72	61	43	32	0%	7	6	4	3	0%	3	2	2	1	1.8	2.1	**0.5**
40-49	2796826	969	2908	3.7%	108	91	65	48	0%	13	11	8	6	0%	9	7	5	4	2.1	2.7	**0.9**
50-59	3256014	917	2751	6.7%	184	156	110	83	1%	25	21	15	11	0%	12	11	7	6	1.1	1.4	**0.2**
60-69	5081118	715	2145	14.3%	308	243	185	139	2%	48	38	29	22	2%	43	34	26	19	1.0	1.3	**0.3**
70-79	3122185	605	1815	28.6%	520	411	312	234	4%	74	58	44	33	9%	163	129	98	74	0.5	0.9	**0.2**
80+	786448	1077	3232	35.5%	1147	929	688	516	3%	101	82	61	46	21%	679	550	407	305	0.4	0.4	**0.2**
TOTAL						1940	1437	1078			221	164	123			733	545	409			

*** Explanation of the models**

Model 1: Effectiveness Vaxzevria (18-64 years of age=85%;65-79 years of age= 79%;>80 years of age=81% (Bernal et al., Vasileiou et al.))
Model 2: Effectiveness Vaxzevria is assumed to start from three weeks onwards (18-64 years of age=85%;65-79 years of age=79%;>80 years of age=81%)
Model 3: Effectiveness Vaxzevria is assumed to start from three weeks onwards (60% effectiveness (pre-licensing trial))
Model 4: No underreporting of TTS cases to EudraVigilance
Model 5: Sensitivity analysis for underreporting of TTS cases to EudraVigilance (0% first 7 days; 20% between day 8 and day 14; 50% after day 14)