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Public's perspective on COVID-19 adenovirus vector vaccines after thrombosis with thrombocytopenia syndrome (TTS) reports and associated regulatory actions – A cross-sectional study in six EU member states

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ABSTRACT

Objective: In 2021, thrombosis with thrombocytopenia syndrome (TTS) was confirmed by the European Medicines Agency (EMA) as a rare side effect of the COVID-19 adenovirus vector vaccines Vaxzevria® and Jcovden®. This study aimed to describe the public's knowledge of TTS and how it affected the willingness to be vaccinated with COVID-19 vaccines and other vaccines in six European countries.

Methods: From June to October of 2022, a multi-country cross-sectional online survey was conducted in Denmark, Greece, Latvia, Netherlands, Portugal, and Slovenia. The minimum target of participants to be recruited was based on the size of the country's population. The results were analysed descriptively.

Results: In total, 3794 respondents were included in the analysis; across the six countries, 33.3 %–68.3 % reported being familiar with signs and symptoms of TTS, although 3.1–61.4 % of those were able to identify the symptoms correctly. The reported changes in willingness to be vaccinated against COVID-19 and with other vaccines varied per country. The largest reported change in the willingness to be vaccinated with Vaxzevria® and Jcovden® was observed in Denmark (61.2 %), while the willingness to be vaccinated with other COVID-19 vaccines changed most in Slovenia (30.4 %). The smallest decrease in willingness towards future vaccination against COVID-19 was reported in the Netherlands (20.9 %) contrasting with the largest decrease observed in Latvia (69.1 %).

Conclusion: Knowledge about TTS seemed to have influenced the public's opinion in Europe resulting in less willingness to be vaccinated with Vaxzevria® and Jcovden®. Willingness for vaccination against COVID-19 with other vaccines and widespread use of vaccines to prevent other diseases also differed and seemed to be determined by the approaches taken by national health authorities when reacting to and communicating about COVID-19 vaccination risks. Further investigation of optimal risk communication strategies is warranted.

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1. Introduction

In March and April 2021, reports emerged of the serious adverse reaction thrombosis with thrombocytopenia syndrome (TTS) in persons who had been vaccinated against COVID-19 with the SARS-CoV-2 adenovirus vector vaccines Vaxzevria® (from AstraZeneca) and Jcovden® (from Janssen) [1,2]. Many regulators across the globe were prompted to react to this safety signal. In Europe, after confirmation of the rare side effects, the European Medicines Agency (EMA) updated the product information and provided recommendations to learned societies and healthcare professionals to monitor people with signs and symptoms of TTS after being vaccinated with these two vaccines [3]. In addition, the EMA published safety updates on these vaccines, highlights from expert meetings, and news items on its website [4–21]. During 2021 the EMA issued several documents and updates on the vaccines Vaxzevria® and Jcovden® in relation to TTS. These included Direct Healthcare Professional Communication (DHPC), safety updates, and changes to the Summary of Product Characteristics (SmPC) and Package Leaflets (PL) (Fig. 1) [4–21].

Following these regulatory actions, health authorities in the European Union (EU) and European Economic Area (EEA) member states altered national COVID-19 vaccination policies. Many countries opted to pause vaccination with these products until EMA's assessment of the emerging side effect was published but most countries started vaccinating again once additional information became available about the associated TTS risk [22]. Overview of vaccination timelines for the Covid-19 vaccine Vaxzevria® and Jcovden® in six European countries (Denmark, Greece, Latvia, Netherlands, Portugal, and Slovenia) are displayed in *Supplementary materials*, *Fig. S1* and *Fig. S2*.

Research to date is sparse on how the public reacted to the TTS safety issue and how the intentions or willingness to be vaccinated against COVID-19 were affected. Two studies from the US investigated the public reaction to the pause of Jcovden® [23,24]. The first large-scale study which assessed public reactions before, during, and after the pause of Jcovden® showed a widespread loss of trust in the vaccine across respondents with different demographic characteristics, which persisted over time and even after lifting the halt [23]. The other US large-scale study surveyed unvaccinated Americans and showed that within 66 % of respondents who were aware of the pause, 44 % identified blood clots as the reason thereof without prompting. The impact of the temporary halt on vaccine behaviour and perceptions towards the vaccine safety system was mixed and modified by trust in public health authorities. Those who were less willing to be vaccinated due to the pause were also less inclined to be vaccinated against COVID-19 with any vaccine, not only Jcovden® [24].

No research has been published about how the EMA information about TTS from 2021, and changes to national vaccination policies with Vaxzevria® or Jcovden®, affected the public vaccination perceptions in the European region. Therefore, in 2022, the EMA commissioned a multi-country survey in six European countries (Denmark, Greece, Latvia, Portugal, The Netherlands, and Slovenia) to evaluate the impact of the regulatory actions for Vaxzevria® and Jcovden®, following the 2021 safety review, on public vaccination willingness and knowledge about TTS. COVID-19 vaccination coverage and authorities' reactions to the TTS safety issues varied widely across these six European countries [22,25]. Portugal had a remarkably high vaccination coverage (95 %), followed by Denmark (82 %), Greece, and Latvia (both in the range of 71–74 %), trailed by Slovenia (58 %) [25]. Authorities' changes to the national vaccination policies ranged from adjustments to recommendations for vaccination target age groups and/or gender recommended for vaccination (Greece, the Netherlands, Portugal), allowing pregnant women to switch vaccine type in the second vaccination (Latvia), contraindicating vaccines to certain patient groups (Slovenia), to suspending these vaccines from the national vaccination programme soon after the causal link between vaccines and TTS were confirmed (Denmark) [22]. It can, therefore, be expected that variations exist as to how the public was informed and reacted to the news of TTS risk associated with COVID-19 vaccination with these vaccines.

Hence, this article describes the public's perspective on the COVID-19 adenovirus vector vaccines and TTS in the six above mentioned member states of the European Union. Specifically, the aim was twofold, first to describe the public's knowledge and sources of information about TTS, and secondly, to gauge the public's perception of the impact of TTS on the willingness to be vaccinated in the future.

2. Materials and methods

2.1. Study design and data collection

A multi-country cross-sectional descriptive questionnaire survey was conducted [22]. The questionnaire was developed in English, then jointly reviewed, then translated into Dutch, and pilot tested in the Netherlands to assess essential ambiguities in the questions and improve the survey quality. The questionnaire's content was developed to ensure content validity at the EU level. The validity of translations across the six countries was ensured through concurrent forward translations conducted by two professionals from the panel of researchers involved at national level. Bearing these aspects in mind, we considered that a single pilot test would suffice to uncover any weakness in the design. The improved questionnaire was adjusted first in English, and further translated into the language(s) of the participating countries, following a translation protocol, where a native speaker who was not involved in the study team independently reviewed each translated survey.

The questionnaire had both closed and open-ended questions. However, the present paper only describes the results from close ended questions. The variables of interest covered in the questionnaire and addressed in the study were:

(1) Demographic characteristics of respondent: age, gender, belonging to a risk group for COVID-19, and/or a professional group with vaccination priority according to the national vaccination policy.
(2) Present status of vaccination against COVID-19

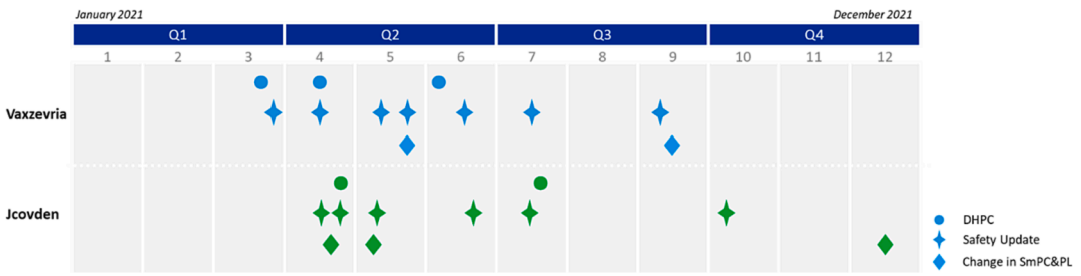

Fig. 1. Overview of EMA communications regarding the Covid-19 vaccines Vaxzevria® and Jcovden®, during 2021 divided into twelve months (1–12) and four quarters (Q1, Q2, Q3, Q4).*DHPC = Direct healthcare professional communications. SmPC = Summaries of Product Characteristics PL = Package leaflet.*

(3) Awareness and perceptions about the risk for TTS from SARS-CoV-2 adenovirus vector vaccines.
(4) Source of information about the risk for TTS.
(5) Awareness about changes in COVID-19 vaccination policy due to TTS in the country, and the perceived impact of these vaccination policy changes on own attitudes towards vaccination, namely:
   a. Changes to own attitudes towards vaccination against COVID-19 and use of COVID-19 vaccines;
   b. Changes to own attitudes towards vaccination programmes in general;
   c. Willingness to receive future (booster) vaccination(s) against COVID-19.

To help respondents recollect the information (i.e., changes in national vaccination policies due to risk for TTS from SARS-CoV-2 adenovirus vector vaccines) and to avoid any confusion with ongoing national vaccination policies, national timelines providing the context and date of the changes referred were developed and incorporated into the questionnaire. Furthermore, questions were specifically formulated to include prompting phrases such as 'before the changes' and 'after the changes' [22]. The final questionnaires in the English version can be consulted in the *Supplementary material*.

2.2. Recruitment

Each of the six participating countries selected the most suitable strategy to obtain a sample as representative as possible of their country's adult population. Recruitment strategy details across various countries are displayed in *Supplementary materials*, *Table S1*. The minimum target of citizens to be recruited was linked to the country's population size, aiming to include at least 100–200 participants per country, which was expected to be sufficiently large to display the variety in attitudes (Table 1).

The web-based questionnaires were hosted either nationally (Denmark, the Netherlands and Slovenia) or by Utrecht University (Greece, Latvia, and Portugal). In the latter option, Utrecht University provided the digital platform for other countries, but each country team was responsible for the dissemination and implementation at national level. The platform to develop and run questionnaires were: Qualtrics via Utrecht University for Greece, Latvia and Portugal, I&O Research for the Netherlands, SurveyXact for Denmark and 1 ka for Slovenia [22].

2.3. Data analysis

Descriptive analyses were conducted. For categorical variables, frequencies and percentages were reported. For continuous variables mean and standard deviation (SD), or median and range (minimum, maximum) were reported. Only valid entries of the respondents were included in the analysis, namely those who provided informed consent as well as all sociodemographic information (e.g., sex, age, occupation), and at least one response to COVID-19 vaccine-related questions. Respondents who were healthcare professionals were excluded from the analysis. Results report the number of respondents for each question. Each country team was responsible for analysing their national data. Analyses were conducted using R version 4.2.0 (Greece, Latvia, the Netherlands, Portugal), IBM SPSS Statistics (Version 28) (Denmark, Slovenia), and Excel 2016 (Denmark). For the countries running analysis using R, attempts were made to harmonize analysis by developing common R scripts and templates for data presentation [22].

Table 1
Target sample size in different countries.

Member State (Million inhabitants)	Minimum target of completed questionnaires
Latvia (1.9)	100
Slovenia (2.1)	100
Denmark (5.9)	150
Portugal (10.3)	175
Greece (10.6)	175
Netherlands (17.3)	200
TOTAL (48.1)	900

2.4. Ethical considerations

Specific requirements for ethical approval for research and data protection regulations were addressed, considering national and European settings. Following national laws, the approvals for the ethics boards were waived (Denmark, the Netherlands) or granted (Portugal, Greece, Slovenia, Latvia).

3. Results

3.1. Characteristics of respondents

From a total of 4343 citizens who responded to the surveys, 3794 had valid entries and were included in the analysis. The number and characteristics of the respondents in each country are summarized in Table 2. Most respondents were female (66.3 %–80.6 %) across all countries except for Slovenia. All countries had participants from all age groups, except for Slovenia where no participants older than 80 were registered. Participants from Greece and Latvia were the youngest with an average age of 45 years (SD = 16.6) and 42 years (SD = 12.9), respectively, and participants from Denmark and the Netherlands were the oldest with an average age of 53 years (SD = 15.6) and 54 years (SD = 17.1), respectively. More than half of the participants had a higher education (University undergraduate, postgraduate, and higher) in Denmark (59.2 %), Greece (64.2 %), Latvia (71.5 %), and Portugal (63.6 %). Although not more than half but still the largest number of respondents were highly educated in the Netherlands (40.0 %) and Slovenia (48.6 %).

Across all countries, more than half of the participants had received at least one vaccine dose against COVID-19. Countries with the highest proportion of non-vaccinated participants were Latvia (43.7 %) and Slovenia (26.2 %).

3.2. Knowledge and sources of information about TTS

Participants' knowledge and sources of information about TTS are shown in Table 3.

Most participants (74.8–93.5 %) were aware of TTS risk associated with Vaxzevria® or Jcovden®. The highest level of awareness was found in Portugal with only 6.5 % being unaware of the risk. The lowest was found in Greece where 25.2 % remained unaware about TTS.

The main sources of information about TTS were mainstream media, i.e., televised press conferences held by authorities (78.2 % in Denmark, 65.2 % in Greece, 69.9 % in the Netherlands, 86.1 % in Portugal, and 75.5 % in Slovenia). In Latvia, internet e.g., news portals, were the key information source about TTS (57.3 %). Internet was also reported as an important source in the other countries (28.4–43.1 %). Furthermore, social media was reported as a valuable information source (12.8–42.5 %) in all countries except for Greece (4.5 %). Healthcare professionals made a modest contribution as information providers.

In all countries, 33.3–68.3 % of participants reported being familiar with signs and symptoms of TTS although of those many were not able to identify its exact symptoms. The least known symptom was *A headache that feels worse when you lie down or bend over* which was only identified by 3.1 % of the participants in the Netherlands who reported being familiar with the signs and symptoms of TTS. The most known symptom was *Shortness of breath, chest pain, leg swelling, or persistent abdominal pain* identified by 61.4 % of the participants in Greece who reported being familiar with the signs and symptoms of TTS.

Table 2
Characteristics of study respondents in different countries (N = 3794).*

	Denmark		Greece		Latvia		Netherlands		Portugal		Slovenia	
Total N	211		193		719		492		1611		568	
Gender												
N (%)*												
Male	53	(25.1)	63	(32.6)	154	(21.4)	242	(49.2)	305	(18.9)	290	(51.1)
Female	154	(73.0)	128	(66.3)	527	(73.3)	248	(50.4)	1298	(80.6)	275	(48.4)
Other gender identity	4	(1.9)	1	(0.5)	5	(0.7)	0	(0.0)	2	(0.1)	2	(0.4)
Rather not say	0	(0.0)	1	(0.5)	33	(4.6)	2	(0.4)	6	(0.4)	1	(0.2)
Age												
Average age (SD)	53	(15.6)	45	(16.6)	42	(12.9)	54	(17.1)	48	(12.3)	48	(15.3)
Age range	19–93		18–82		18–87		18–90		18–82		19–79	
Age categories												
N (%)*												
18–30	23	(10.9)	76	(39.4)	139	(19.3)	59	(12.0)	173	(10.7)	89	(15.7)
31–40	20	(9.5)	41	(21.2)	205	(28.5)	67	(13.6)	134	(8.3)	102	(18.0)
41–50	43	(20.4)	40	(20.7)	196	(27.3)	53	(10.8)	504	(31.3)	147	(25.9)
51–60	50	(23.7)	22	(11.4)	131	(18.2)	94	(19.1)	565	(35.1)	82	(14.4)
61–70	46	(21.8)	11	(5.7)	32	(4.5)	126	(25.6)	220	(13.7)	96	(16.9)
71–80	27	(12.8)	1	(0.5)	11	(1.5)	81	(16.5)	14	(0.9)	52	(9.2)
80+	2	(0.9)	2	(1.0)	5	(0.7)	12	(2.4)	1	(0.1)	0	(0.0)
Educational level												
N (%)*												
Primary school, secondary school	27	(12.8)	40	(20.7)	88	(12.2)	141	(28.7)	344	(21.4)	188	(33.1)
Professional school	54	(25.6)	24	(12.4)	101	(14.0)	145	(29.5)	41	(2.5)	89	(15.7)
University undergraduate, postgraduate and higher	125	(59.2)	124	(64.2)	514	(71.5)	197	(40.0)	1025	(63.6)	276	(48.6)
Other	5	(2.4)	5	(2.6)	16	(2.2)	9	(1.8)	201	(12.5)	15	(2.6)
Vaccination status												
N (%)*												
Not vaccinated	24	(11.4)	17	(8.8)	314	(43.7)	44	(8.9)	73	(4.5)	149	(26.2)
Vaccinated	186	(88.2)	173	(89.6)	361	(50.2)	447	(90.9)	1526	(94.7)	414	(72.9)
Prefer not to say	1	(0.5)	3	(1.6)	44	(6.1)	1	(0.2)	12	(0.7)	5	(0.9)

* Due to rounding, percentages might not add up to 100%.

3.3. Perception of impact of TTS on the willingness to be vaccinated

Participants were asked whether their willingness to receive Vaxzevria® or Jcovden® had changed after hearing about their association with the risk of TTS. Similarly, they reflected whether their willingness to receive another COVID-19 vaccine was altered after changes to the national COVID-19 vaccination programmes due to the side effects of Vaxzevria® or Jcovden® (Fig. 2).

In Denmark (61.2 %), Greece (44.2 %), and Portugal (48.9 %) most participants indicated that their willingness to be vaccinated with Vaxzevria® or Jcovden® had changed after hearing about TTS. In Latvia (50.2 %) and the Netherlands (48.2 %), most participants indicated not to have changed their willingness to be vaccinated with Vaxzevria® or Jcovden® after hearing about TTS. In Slovenia, the percentage of those who reported changes in willingness to be vaccinated (38.8 %) was remarkably similar to those who indicated no change (38.7 %).

When looking into participants' willingness to receive another COVID-19 vaccine when hearing about the changes to the vaccination programme due to TTS risk, most participants reported no changes in their willingness. The largest proportions of respondents stating that it also changed their willingness to receive another vaccine were found in Latvia (28.8 %) and Slovenia (30.4 %).

Lastly, the respondents were asked whether they were less willing to be vaccinated or whether their trust in COVID-19 vaccines had decreased after learning about TTS (Fig. 3).

In Latvia (69.1 %) and Slovenia (51.6 %) more than half of the participants were less willing to be vaccinated against COVID-19 in the future after the reports of the side effects, while less than 30 % of respondents mentioned so in Denmark, the Netherlands, and Portugal. In Greece, the distribution of respondents who were less willing to be COVID-19 vaccinated in the future and those who were not affected in their trust was almost the same: 31.4 % and 37.3 %, respectively. The proportions of respondents who lost trust in COVID-19 vaccines were similar to the proportions of respondents who were less willing to get vaccinated.

4. Discussion

This study aimed to describe public awareness of TTS as a side effect of the SARS-CoV-2 adenovirus vector vaccines, Vaxzevria® and Jcovden®, and assess how this awareness affected public trust and willingness to get vaccinated with these and other COVID-19 vaccines in six European countries, with various COVID-19 vaccination coverage and diverse reactions by national authorities to the information disseminated by EMA about TTS in 2021. The study showed that most of the public in all countries seemed to be aware of the TTS risk, despite differences in healthcare systems, cultures, and COVID-19 vaccination policies.

This study demonstrated that in most countries mainstream media dissemination of information to a wide audience through broadcast television, radio, or newspapers, was the most important communication channel when spreading rapid official news, such as national vaccination policy changes during the COVID-19 pandemic, in most countries. In Denmark, Greece, Netherlands, and Portugal this included televised press conferences held routinely by several authorities. Thus, television seemed to be the most important mainstream media channel during this pandemic crisis.

Especially in times of isolation, social media became a valuable means to remain close to others and to discuss relevant information, including updates and reasons for COVID-19 vaccination policies and their changes. However, the spread of misinformation in social media and other digital platforms has been deemed a threat to public health [26]. In this survey, this was evident in Latvia, where the most frequently used information source about TTS was social media and COVID-19 vaccination coverage was the lowest and the mistrust in COVID-19 vaccines was the highest when compared to all the other surveyed countries. However, controlling the social media narrative is not a way to increase trust in vaccines. In contrast, as demonstrated in an Australian study, controlling access to or censoring vaccine-critical misinformation does not reduce vaccine-critical narratives; instead, Facebook bans of vaccine-critical users encourage movement to other

Table 3
Participants' knowledge and sources of information about TTS in different countries.

	Denmark		Greece		Latvia		Netherland		Portugal		Slovenia	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Awareness of TTS associated with Vaxzevria® and Jcovden®												
*All respondents**	**129**		**151**		**565**		**492**		**1160**		**517**	
Yes	110	(85.3)	113	(74.8)	513	(90.8)	394	(80.1)	1085	(93.5)	440	(85.1)
No	19	(14.7)	38	(25.2)	52	(9.2)	98	(19.9)	75	(6.5)	77	(14.9)
Source of information about TTS												
*All respondents**	**110**		**132**		**499**		**492**		**1078**		**440**	
General Practitioner/Family Doctor before deciding to get a vaccination	5	(4.5)	17	(12.9)	21	(4.2)	5	(1.0)	40	(3.7)	27	(6.1)
Pharmacy	1	(0.9)	6	(4.5)	7	(1.4)	1	(0.2)	5	(0.5)	12	(2.7)
Specialist Physician, such as a Vascular Surgeon or an Internal Medicine Specialist.	3	(2.7)	10	(7.6)	37	(7.4)	6	(1.2)	22	(2.0)	27	(6.1)
Another healthcare professional before deciding to get a vaccination	6	(5.5)	16	(12.1)	28	(5.6)	5	(1.0)	45	(4.2)	35	(8.0)
At the vaccination centre by a health professional	3	(2.7)	4	(3.0)	8	(1.6)	1	(0.2)	28	(2.6)	16	(3.6)
I filled in a medical history form and became aware of this risk	0	(0.0)	5	(3.8)	13	(2.6)	3	(0.6)	28	(2.6)	15	(3.4)
Family and friends	33	(30.0)	41	(31.1)	174	(34.9)	79	(16.1)	164	(15.2)	149	(33.9)
Mainstream media (TV, radio, newspapers)	86	(78.2)	86	(65.2)	234	(46.9)	344	(69.9)	928	(86.1)	332	(75.5)
Social media such as Facebook, LinkedIn, Twitter, or Instagram	27	(24.5)	6	(4.5)	212	(42.5)	63	(12.8)	208	(19.3)	133	(30.2)
I read the package leaflet/patient information leaflet	6	(5.5)	42	(31.8)	145	(29.1)	10	(2.0)	98	(9.1)	36	(8.2)
I found information on the Internet (e.g., news portals, etc.)	46	(41.8)	54	(40.9)	286	(57.3)	146	(29.7)	465	(43.1)	125	(28.4)
At work	10	(9.1)	18	(13.6)	20	(4.0)	33	(6.7)	217	(20.1)	26	(5.9)
This questionnaire	1	(0.9)	2	(1.5)	6	(1.2)	3	(0.6)	6	(0.6)	4	(0.9)
Familiar with signs and symptoms of TTS												
*All respondents**	**109**		**132**		**496**		**394**		**1078**		**440**	
Yes	51	(46.8)	44	(33.3)	339	(68.3)	159	(40.4)	542	(50.3)	204	(46.4)
No	58	(53.2)	88	(66.7)	157	(31.7)	235	(59.6)	536	(49.7)	236	(53.6)
Identified symptoms of TTS**												
*All respondents**	**51**		**44**		**329**		**159**		**536**		**204**	
A severe headache that is not relieved with painkillers or is getting worse	19	(37.3)	9	(20.5)	108	(32.8)	25	(15.7)	153	(28.5)	125	(61.3)
A headache that feels worse when you lie down or bend over	9	(17.6)	3	(6.8)	50	(15.2)	5	(3.1)	46	(8.6)	42	(20.6)
A headache that is unusual along with blurred vision, feeling or being sick, problems speaking, weakness, drowsiness, or seizures (fits)	21	(41.2)	21	(47.7)	193	(58.7)	50	(31.4)	206	(38.4)	122	(59.8)
A rash that looks like small bruises or bleeding under the skin	18	(35.3)	13	(29.5)	162	(49.2)	43	(27.0)	178	(32.2)	56	(27.5)
Shortness of breath, chest pain, leg swelling, or persistent abdominal pain	18	(35.3)	27	(61.4)	177	(53.8)	52	(32.7)	189	(35.3)	125	(61.3)
Nausea	7	(13.7)	7	(15.9)	52	(15.8)	12	(7.5)	72	(13.4)	80	(39.2)
I do not know/I am not sure	17	(33.3)	8	(18.2)	57	(17.3)	58	(36.5)	157	(29.3)	18	(8.8)
Identified all symptoms correctly	2	(3.9)	2	(4.5)	3	(0.9)	0	(0.0)	1	(0.2)	3	(1.5)

*Respondents who answered that question.
**All symptoms are potential signs of TTS.

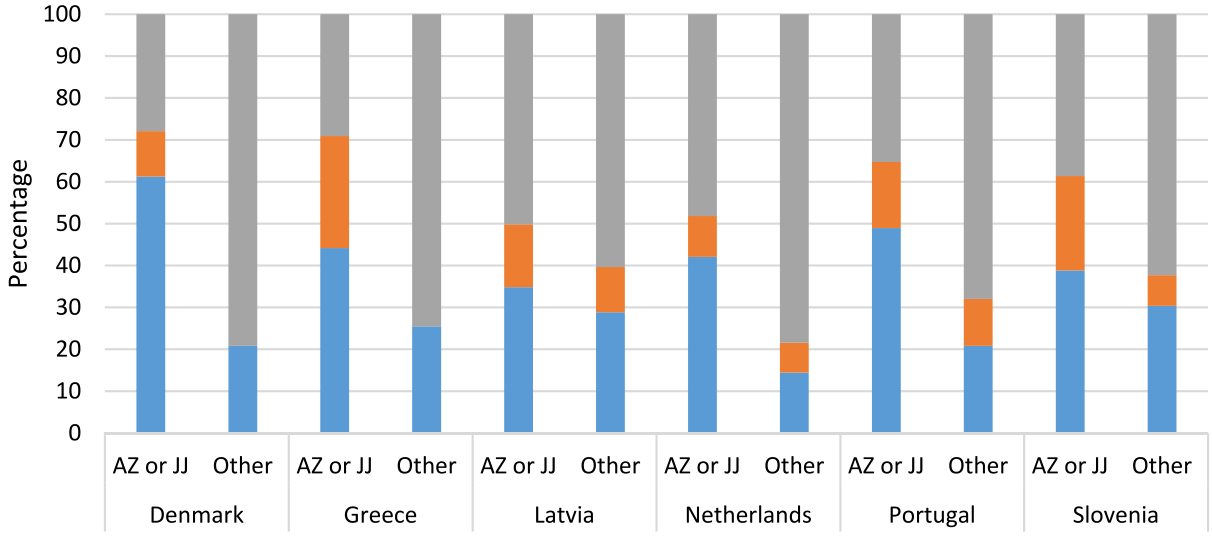

Fig. 2. Changes to participants' willingness to receive COVID-19 vaccines after hearing about TTS in different countries. 'AZ or JJ'= Vaxzevria® and Jcovden®. 'Other' = other COVID-19 vaccines than Vaxzevria® and Jcovden®. Change in willingness. I am not sure. Willingness did not change. (Denmark N = 129, Greece N = 172, Latvia N = 574, Netherlands N = 492, Portugal N = 1179, Slovenia N = 520).

potentially radicalizing platforms [27].

Another pattern observed in this study for all the countries was that family and friends were crucial in sharing information, while healthcare professionals seemed to have a very modest role when gaining knowledge about SARS-CoV-2 adenovirus vector vaccines and their side effects. This finding, similar to the social media effects, could increase the risk of misinformation being spread. Our results, demonstrating that many participants reported being very aware of TTS and its association

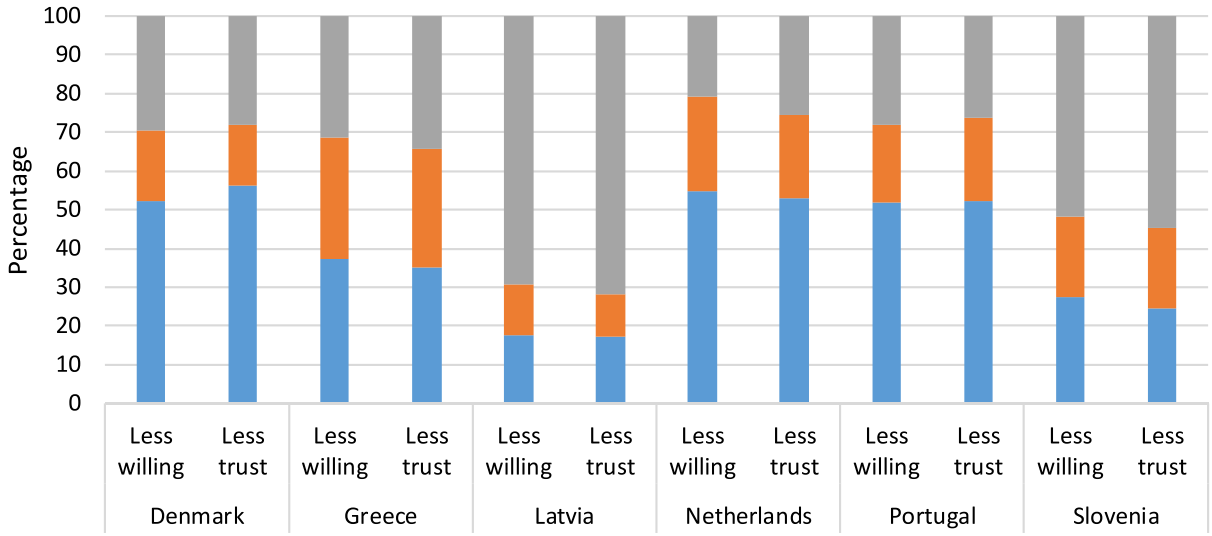

Fig. 3. Potential changes in participants' willingness and trust after reports of side effects from Vaxzevria® and Jcovden®. 'Less willing' = I am less willing to get vaccinated against COVID-19 in the future. 'Less trust' = I have less trust about the safety of COVID-19 vaccines. Ratings are defined as: Disagree and disagree completely Neither agree nor disagree Agree and agree completely. (Denmark N = 128, Greece N = 169, Latvia N = 528, Netherlands N = 492, Portugal N = 1147, Slovenia N = 517).

with Vaxzevria® and Jcovden® but were not familiar with TTS symptoms, is in line with the speculation, that misinformation, or incomplete information about TTS, could be spread also through close social networks. Thus, to avoid vaccination hesitancy and maintain public trust in vaccines, the official information being communicated through mainstream media seem of crucial importance.

In addition to the channel, the content and the format in which information is provided by authorities are essential for the public trust in vaccines. Research on the impact of official COVID-19 information communication by national authorities on public trust in vaccines shows that communicating with certainty is not always a good strategy [28]. Certainty when providing official information may reduce vaccination intentions and public trust when conflicting information emerges, which was exactly the case with SARS-CoV-2 adenovirus vector vaccines, where fatal TTS events were reported alongside all the proven beneficial effects of the vaccine [29]. As the results of this study show, the way the national authorities approached and communicated such uncertainties may have had an impact on the public trust in the COVID-19 vaccines Vaxzevria® and Jcovden®, and on other COVID-19 vaccines. For most respondents, the information about TTS reports negatively affected their willingness to be vaccinated with Vaxzevria® and Jcovden® as well as other COVID-19 vaccines in the future, indicating that the information about risks associated with vaccines was considered by the public.

It is likely that national vaccination policy changes and communication thereof might have had an impact on the public perceptions of both the SARS-CoV-2 adenovirus vector and other COVID-19 vaccines. In Denmark specifically, an approach of "radical transparency" was adopted, whereby vaccine information was transparently disclosed to the public, even if negative information could decrease vaccine uptake. According to Petersen et al., transparent negative communication about vaccines may harm vaccine acceptance here and now, but at the same time, it may increase trust in health authorities [30]. Supporting Petersen et al., this study shows that in Denmark, where the SARS-CoV-2 adenovirus vector vaccines were withdrawn from the national vaccination programme due to TTS risk, thus openly acknowledging the severity of the side effect, the proportion of the respondents reporting that their willingness to get vaccinated with these vaccines had changed, was larger than in any other country. Notably, the proportions of respondents reporting changes in willingness to receive other vaccines, as well as those reporting less willingness and trust in other vaccines, in the Danish sample were among the lowest.

Similar tendencies were also seen in Portugal, where the population traditionally is very receptive to vaccination. In Portugal, for "precautionary reasons", a decision was made to pause COVID-19 vaccination with Vaxzevria® after the reports about TTS and then televised and widely shared on social media. This changed the Portugal citizens' willingness to be vaccinated with COVID-19 vector vaccines, but most of the respondents kept their trust in the safety of other COVID-19 vaccines as well as their willingness to get vaccinated against COVID-19 in the future. Similar trends were observed in the Netherlands, where willingness towards adenoviral vector vaccination markedly decreased, but willingness to use other COVID-19 vaccines in the future, and overall trust in the safety of vaccines remained stable.

A different picture, however, was observed in Greece, where there was no interruption of vaccination with COVID-19 vaccines, but instead, several changes in the vaccination process were introduced. This could cultivate uncertainty about COVID-19 vaccines' safety in general. Such tendency is supported by the study findings showing large proportions of Greek respondents doubting their trust and willingness to be COVID-19 vaccinated in the future. In Latvia and Slovenia, a decrease in willingness to receive both vector vaccines as well as other COVID-19 vaccines was observed, this could be explained by a substantial portion of participants being vaccine-hesitant.

4.1. *Methodological considerations*

This is the first study to measure the EU populations' awareness of TTS and the responses to this side effect in terms of trust in the COVID-19 vaccines. This study has had both methodological strengths and limitations. The strength is that the findings have a broad coverage, as the study was conducted across six EU member states with a wide geographic spread, contrasting healthcare systems and cultures, and a wide variation in vaccination policies following the EMA recommendations. The reported vaccination status among study respondents corresponded well with that of the national statistics [25], in four out of six countries. This underscores the belief that the results were not jeopardized by extreme views on vaccines. A limitation, however, is that despite efforts made in the participating countries to recruit a representative sample, some selection bias may have occurred, as survey distribution varied across the six countries, using both citizen panels and social media. Consequently, besides the already mentioned large proportions of not vaccinated respondents in Latvia and Slovenia, women

and the middle-aged were the majority among study participants, which is not totally in accordance with the gender and age distribution of the national populations. Moreover, several questions were left incomplete in the survey, which may lead to potential non-response bias [31].

Another limitation is recall bias, which could be a concern as there were no baseline measurements and all parameters had to be ascertained retrospectively. To minimize any effect from recall bias, we included a visual cue of the national timelines (of activities, events, and policy changes) to provide the respondents with the context of 2021 when the vaccination campaign changes following TTS reports were implemented. The direction of the bias would most likely be that respondents would recall the TTS safety information as being less worrying or that they recalled being more willing to be vaccinated in 2021 than they actually were as the pandemic aftermath revealed most vaccines had low rates of adverse drug reactions and contributed towards opening society. It is also likely that awareness about TTS would have been overestimated retrospectively, due to social desirability.

5. Conclusions

Our study found that while the public was aware of TTS, participants had limited knowledge about its signs and symptoms. For most of the public, the information about TTS negatively affected their wish to be vaccinated with Vaxzevria® and Jcovden® in the future, indicating that the information about risks associated with these vaccines was considered. However, differences between the countries in public trust and willingness to be vaccinated against COVID-19 or to use other vaccines in the future were also observed. This could be the consequence of general perceptions towards vaccines and health authorities as well as different approaches by health authorities across different countries, as to how they communicated the risks associated with COVID-19 vaccination and how they introduced changes to national vaccination programmes. Further investigation of optimal risk communication by national authorities to maintain public trust is warranted.

CRediT authorship contribution statement

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Teresa Leonardo Alves reports financial support was provided by European Medicines Agency.

Data availability

The authors do not have permission to share data.

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All authors have read and agreed to the published version of the manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2023.12.065.

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