RiskAware TTS

Impact of EU label changes and regulatory communication on SARS-CoV-2 adenovirus vector vaccines in context of thrombosis with thrombocytopenia syndrome (TTS): risk awareness and adherence

1 Abstract

1.1 RiskAware TTS

Impact of EU label changes and regulatory communication on SARS-CoV-2 adenovirus vector vaccines in context of thrombosis with thrombocytopenia syndrome (TTS): risk awareness and adherence (RiskAware TTS).

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1.2 Keywords

SARS-CoV-2 adenovirus vector vaccines; COVID-19; thrombosis with thrombocytopenia syndrome; risk awareness; vaccination

1.3 Rationale and background

The European Medicines Agency (EMA) has provided recommendations in 2021 to learned societies and healthcare professionals when assessing people with signs and symptoms of thrombosis with thrombocytopenia syndrome (TTS) after being vaccinated with adenovirus vector vaccines Vaxzevria or Jcovden.
In addition, the EMA also published safety updates on these vaccines, highlights from expert meetings and news items on its website.

1.4 Research question and objectives

The study presented in this report aimed to evaluate the impact of the regulatory actions for Vaxzevria and for Jcovden following the 2021 safety review. The study's objectives were:

1. To determine the extent of how regulatory actions for thrombosis with thrombocytopenia syndrome (TTS) have changed national vaccination policy
2. To determine the level of healthcare professional awareness and knowledge of the risk of TTS and their adherence to Summary of Product Characteristics (SmPC) recommendations for SARS-CoV-2 adenovirus vector vaccines

3. To determine the extent of change in healthcare professionals´ attitudes towards COVID-19 national vaccination campaigns and recommendations
4. To determine the extent of change in citizens' attitudes towards vaccination against SARS-CoV-2

1.5 Study design

The study had a qualitative approach and was composed of three work packages involving a literature review, web-based questionnaires, and semi-structured interviews.
Work package 1 (WP1) compiled an overview and timeline for national COVID-19 vaccination policies and any changes thereof prompted by the TTS risk communication. This included changes to national vaccination policies, defining risk group(s), age group(s) prioritization, and recommendations for second vaccine dose or for other SARS-CoV-2 vaccines. The methodology in Work package 1 comprised a review of available (grey) literature and policy documents to identify the events and changes in vaccination policies in the countries participating in this study.

In Work package 2 (WP2), we investigated the impact of the regulatory measures and communication on the changes that occurred in national vaccination policies, on healthcare professionals (HCPs) and experts who have been actively involved either in the vaccination against COVID-19, in the provision of information about its risks, or in the monitoring and treatment of side-effects thereof. The methodologic approach in Work package 2 included web-based questionnaires and semi-structured interviews.

In Work package 3 (WP3), we investigated the impact of the measures and of the changes in vaccination policies on citizens eligible to be vaccinated against COVID-19. The methodologic approach in Work package 3 included web-based questionnaires.

1.6 Setting

The multi-country study was conducted in six member states of the European Union: Denmark (DK), Greece (GR), Latvia (LV), Netherlands (NL), Portugal (PT) and Slovenia (SI).

1.7 Subjects and study size

In **work package 1**, policy decisions from six EU member states were covered (DK, GR, LV, NL, PT, SI).

In **work package 2,** we surveyed 1659 healthcare professionals in five EU member states (GR, LV, NL, PT, SI)[1], 1555 provided informed consent and a total of 914 were included in the analysis. 565 healthcare professionals filled in all the questions. Approximately 38% of the questionnaires were incomplete. We interviewed 41 professionals in six EU member states (DK, GR, LV, NL, PT, SI). From these, 23 were healthcare professionals and other 18 were experts. Table 1 outlines the distribution of respondents to the healthcare professionals' survey across all participating countries and Table 2 shows the distribution of the interviewees.

[1] In Denmark Vaxzevria and Jcovden were not included in the national vaccination programme and therefore Danish healthcare professionals were not surveyed since they had no experiences they could reflect upon

Table 1. Work package 2: survey HCP

		Greece	Latvia	Netherlands	Portugal	Slovenia	TOTAL
Clicked on survey link		159	140	546	504	310	1659
Provided informed consent		142	122	514	504	273	1555
Included in analysis*		109	103	324	206	172	914
Filled in all questions in survey		69	60	202	119	115	565
Incomplete surveys	*TOTAL (%)***	40 (36%)	43 (41%)	122 (37%)	87 (42%)	57 (33%)	349 (38%)
	Doctor GPs	1	33	50	9	0	93
	Doctor Specialist	32	2	4	3	4	45
	Nurse	1	2	24	25	27	79
	Pharmacist	4	1	13	42	22	82
	Other (includes veterinarians + other open response)	2	5	31	8	4	50

*The following healthcare professionals were excluded: Those not involved in key activities: vaccination administration or coordination, counselling, or monitoring of side-effects), or those that had not fully completed the baseline questions and one outcome question.
**Percentage is the number of incomplete surveys divided by the number included in the analysis

Table 2. Work package 2: Interviews performed per country

Country	Interviewees
Denmark	4 HCPs 6 Experts
Greece	6 HCPs 1 Expert
Latvia	2 HCPs 3 Experts
Netherlands	4 HCPs 5 Experts
Portugal	3 HCPs 2 Experts
Slovenia	4 HCPs 1 Expert
TOTAL	**23 HCPs** **18 Experts**

In **work package 3**, we surveyed 4572 citizens in six EU member states (DK, GR, LV, NL, PT, SI), 4343 provided their informed consent and a total of 3794 were included in the analysis. Approximately 22% of the questionnaires were incomplete. Table 3 showcases the distribution of the survey participants over the countries.

Table 3. Work Package 3: Survey citizens

	Denmark	Greece	Latvia	Netherlands	Portugal	Slovenia	TOTAL
Clicked on survey link	323	247	956	516	1872	658	4572
Provided informed consent	253	229	883	492	1872	614	4343
Included in analysis*	211	193	719	492	1611	568	3794
Filled in all questions in survey	128	169	523	492	1146	511	2969
Incomplete surveys (%)**	83 (39%)	24 (12%)	196 (27%)	0 (0%)	465 (29%)	57 (10%)	825 (22%)

*The following respondents were excluded: those who had not fully completed the baseline questions and one outcome question, and those who reported to be healthcare professionals.

**Percentage is the number of incomplete surveys divided by the number included in the analysis

1.8 Variables and data sources

Variables

In the web-based survey to healthcare professionals (WP2), variables of interest covered were the following:

(1) HCP's own working/vaccination duty context (vaccination centres, pharmacies, own medical practice, hospital).
(2) Source of information about the risk for TTS (through media, professional society, direct healthcare communication, SmPC, instructions from authorities).
(3) Knowledge and awareness about the direct healthcare professional communications (DHPCs).
(4) Whether they have witnessed any TTS cases in their vaccination practice.
(5) Knowledge and awareness of the signs and symptoms of TTS and the need to refer to specialists (e.g., haematologists, specialists in coagulation) to diagnose and treat the condition; any instructions from vaccination authorities and/or national competent authorities for medicinal products and/or clinical practice guidelines when coming across TTS[2].
(6) Provision of information to citizens about the TTS warning signs/symptoms and need to seek further health assistance should they occur.
(7) Knowledge and awareness of (updated) clinical guidelines and recommendations from learned societies for treating TTS (e.g., with anticoagulants) when available/applicable.
(8) Knowledge and awareness of the contraindications to use adenovirus vector vaccines in patients who have experienced TTS following vaccination with Vaxzevria.
(9) Change to attitudes towards the COVID-19 vaccination campaign and national vaccination programme after TTS risk communication.

In the interviews, both healthcare professionals, experts and policy makers involved in (advising about) the decision making of the COVID-19 vaccination campaign were asked about:

[2] Depending on country.

- how they perceived the events and the risk communication about the two adenovirus vector vaccines in their country.
- the views and actions of HCPs / experts regarding Jcovden and Vaxzevria vaccines.
- their concerns, ideas, and questions about the risk communication and the impact thereof.

In the web-based survey to citizens, variables of interest covered were the following:

(1) Respondent characteristics: 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 and period of first/second/booster vaccination.
(3) Vaccine(s) received.[3]
(4) Awareness and perceptions about the benefits and risks of the SARS-CoV-2 adenovirus vector vaccines.
(5) Awareness and perceptions about the risk for TTS from SARS-CoV-2 adenovirus vector vaccines.
(6) Source of information about the risk for TTS.
(7) Awareness about changes in COVID-19 vaccination policy and their impact on own perceptions and attitudes regarding vaccination against COVID-19.
(8) Changes to own attitudes towards vaccination against COVID-19 and use of COVID-19 vaccines: no vaccination against COVID-19, postponement of vaccination, decision to change vaccine.
(9) Changes to own attitudes towards vaccination programmes in general.
(10) Changes to own attitudes towards potential vaccination of their young adult-teenager children against COVID-19.
(11) Willingness to receive future (booster) vaccination(s) against COVID-19.

Data sources

In this study, data were collected, and no established data sources were used.
In Work package 1, data to compile the overview and timeline of COVID-19 vaccination policies in each country were collected through a grey literature review.
In Work package 2, data were obtained through cross-sectional data collection, including a survey among healthcare professionals and semi-structured interviews with healthcare professionals and experts.
In Work package 3, data were obtained through cross-sectional data collection, through a survey among citizens.

1.9 Results

1.9.1 Impact of regulatory actions for TTS on national vaccination policies

We observed a great variability across countries as to the implementation of their vaccination policies and subsequent changes.

In general, there were fewer changes visible for Jcovden when compared to Vaxzevria, but there seems to be a greater variation across countries for the policies concerning Jcovden. This is likely

[3] Our recruitment did not restrict respondents to citizens who had received adenovirus vaccines. We were also interested in finding out whether citizens' choice of vaccine/or their decision not to take vaccine had been affected by the risk communication.

because this vaccine was not available around the same time in each country. For instance, Portugal and Greece had access to this product at a later stage than Denmark or the Netherlands. The working mechanism of these vaccines was already known by the time Jcovden entered the market, whereas Vaxzevria was the first of its kind and any new safety information was more likely to result in changes to the product information and subsequently to vaccination practices.

Changes in the vaccination policies in Denmark often preceded or were simultaneous to EMA risk communication publications.

Although in many countries the vaccination advisory committees followed the recommendations of the EMA, these were not always implemented in the national policies.

1.9.2 Awareness and knowledge about TTS risk among healthcare professionals

An overwhelming majority of healthcare professionals were aware about the reports of TTS associated with COVID-19 adenovirus vector vaccines, with all countries reporting percentages between 85 and 97%.

Most healthcare professionals declared to have become aware about TTS risk in the first quarter of 2021. Approximately half of the healthcare professionals were able to identify the correct risk of developing TTS (i.e., very rare side effect). Approximately half of the healthcare professionals were able to identify women under 60 years old as a group at risk of developing TTS after vaccination. In contrast, men under 60 years old were only identified as risk group by a much smaller percentage of healthcare professionals.

Healthcare professionals were also more likely to identify fatal and serious outcomes from TTS rather than non-serious effects that could be addressed throughout treatment. Half of the healthcare professionals seemed to easily identify severe headaches or headaches with blurred vision, or shortness of breath as likely symptoms, but nausea was not considered relevant by many professionals.

1.9.3 Sources of information about TTS risk among healthcare professionals

Mainstream media, health authorities and peers were the main sources of TTS information. Internet and social media seemed to have played a bigger role in Greece than in other countries.

Experts considered they had had timely access to TTS information and the exchange thereof was perceived as efficient and reliable, albeit short in certain aspects, such as epidemiological data. The information from the EMA was considered by the advisory bodies when providing guidance to the vaccination programmes and in some cases, by practitioners.

In contrast, healthcare professionals often felt overwhelmed by the amount of information received during the pandemic and struggled to cope with frequent updates and changes to the vaccination strategies. During interviews, healthcare professionals expressed their apprehension to the fact that TTS reports and changes to the vaccination policy were first presented in televised press conferences, before the HCPs were informed by competent authorities, or their professional societies on actions to take.

HCPs were mainly using the information communicated in televised press conferences in their practice, as well as the information they received from their own networks or professional societies.

EMA guidance was not perceived as a primary source of information, except moderately for the DHPC, as many reverted towards the use of information from national competent authorities, national guidelines or handbooks that had been tailored to their needs (Denmark, Latvia). Some specialists highlighted the existing gap in treatment guidelines for TTS at national level (Portugal) and called on the EMA and competent authorities to better articulate risk communication with concrete, easy to consult guidelines on how to manage patients with TTS.

Half to two thirds of healthcare professionals were unaware of or did not know about any clinical guidelines or recommendations from learned societies for treating TTS in their country. This was particularly striking for The Netherlands, Portugal, and Slovenia.

1.9.4 Awareness and adherence to measures and use of materials on Vaxzevria by healthcare professionals

We had less respondents answering questions on usage of product information, educational materials, and dedicated guidelines than other sections of the survey.

A relatively small number of healthcare professionals were unaware of the SmPC, with the highest percentage being reported for the Netherlands (approximately 23%). An overwhelming percentage of respondents have studied it in Latvia (96.7%). In other countries, such as Slovenia and Portugal, healthcare professionals were aware it exists but had not used it.

The package leaflet was studied extensively in Latvia and in Greece, but about one third of respondents across all countries reported that they had not used it.

In contrast, the DHPC was studied by healthcare professionals across all countries, with usage percentages between 44% in the Netherlands and 95% in Latvia. It is noteworthy that in the Netherlands and in Greece almost one third of respondents admitted to being unaware of these documents.

Respondents reported extensive use of the national guidelines from health authorities, with the lowest use in Greece and the highest in Latvia and Portugal. This is in line with the results of the interviews, when some healthcare professionals were not familiar with the materials on TTS risk provided by the EMA. They were therefore answering questions regarding the content and format based on the information they were familiar with (e.g., National vaccination strategy).

Towards the future, healthcare professionals declared to be more inclined to use either national guidelines or the DHCP, rather than the SmPC or the package leaflet.

1.9.5 Awareness and adherence to measures and use of materials on Jcovden by healthcare professionals

We had less respondents answering questions on usage of product information, educational materials, and dedicated guidelines than other sections of the survey.

A relatively small number of healthcare professionals were unaware of the SmPC, with the highest percentage being reported for the Netherlands (approximately 24%). An overwhelming percentage of respondents had studied it in Latvia (91%). In other countries, such as Greece and Portugal, it was also amply used. One fifth to one third of healthcare professionals were aware it exists but had not used it in Greece, the Netherlands and Slovenia.

The package leaflet was studied extensively in Latvia and in Greece, but about one third of respondents in the Netherlands, Portugal, and Slovenia reported not to have used it.

In contrast, the DHPC had been studied by healthcare professionals across all countries, with usage percentages between 35% in the Netherlands and 93% in Latvia. It is noteworthy that in the Netherlands and in Greece almost one third of respondents admitted being unaware of these documents.

Respondents reported extensive use of the national guidelines from health authorities, with the lowest use in Netherlands at 75% and the highest in Latvia and Portugal with approximately 95% and 93%, respectively.

Towards the future, healthcare professionals declared to be more inclined to use either national guidelines or the DHCP, rather than the SmPC or the package leaflet.

1.9.6 Change to attitudes among healthcare professionals towards recommendations

Half of the respondents declared to always inform citizens, or usually, about the importance of monitoring health symptoms after vaccination. This grew to almost 2/3 of all respondents after the changes in the recommendations and guidelines. The percentages of those that admitted doing so on occasions or even rarely also dropped after the changes.

Around one third of the respondents declared to inform citizens about the symptoms of TTS and the importance of monitoring those after vaccination. This grew to almost 2/3 of all respondents after the changes in the recommendations and guidelines.

Even before the changes one to two thirds of all healthcare professionals already considered that individuals who are at higher risk of developing TTS were to be administered other vaccines than Vaxzevria or Jcovden; thus the difference was not so sharp as for other recommendations. Nevertheless, it was very visible for Portugal and Greece.

One to two thirds of all respondents mentioned advising patients to seek further assistance should warning signs of TTS occur after vaccination. This increased remarkably to around 75-90% across all countries.

Even before the changes in guidelines and recommendations a large majority of respondents already considered that patients who had experienced TTS following vaccination with Vaxzevria were to be administered other vaccines (other than Vaxzevria and Jcovden). Differences were therefore less pronounced yet still visible.

One third to one half of respondents reported to have alerted patients to the signs and symptoms of thromboembolism and/or thrombocytopenia. After the implementation of changes in guidelines and recommendations this percentage increased to 60-85%.

About one third of healthcare professionals admitted to hardly or occasionally checking for signs of thrombosis in patients with thrombocytopenia within 3 weeks after vaccination. This subset decreased considerably after the changes to the guidelines and recommendations.

Even before the changes in guidelines and recommendations, a large majority of respondents already referred patients diagnosed with thrombocytopenia to specialist within 3 weeks after vaccination. Differences were therefore less pronounced and more visible for Greece and Portugal.

About one third to one half of healthcare professionals admitted to check for signs of thrombocytopenia hardly or only occasionally in patients with thrombosis within 3 weeks after vaccination. This subset decreased considerably after the changes to the guidelines and recommendations, with approximately 60-80% of professionals reporting to frequently investigate for signs.

Even before the changes in guidelines and recommendations a large majority of respondents already referred patients diagnosed with thrombosis to specialist within 3 weeks after vaccination. Differences were therefore less pronounced but still visible, particularly for the Netherlands and Portugal.

1.9.7 Impact of communication measures into professional practice

Guidelines from health authorities on COVID-19 vaccination have impacted the professional practice of half to two-thirds of the healthcare professionals. The DHPC was mentioned by one to two thirds of professionals as well the updates to the SmPC. There were some considerable variations between countries.

Only one third to one half of healthcare professionals admitted having changed their professional practice due to the risk minimisation measures, with the highest percentages reported in Greece and the lowest in Slovenia.

Between 7 and 20% of healthcare professionals reported that barriers to the implementation or usage of communications exist, with less hindrances identified in Latvia and more barriers in Greece. Most respondents reported being unaware of any barriers.

The most frequently mentioned barrier was the overwhelming information flow reaching healthcare professionals during the pandemic. They were unable to read and compare all the information that was being received from various sources and subject to recurring changes. A subgroup of respondents also stated that information from credible sources/channels arrived at later stage, often being preceded by ample media coverage.

1.9.8 Overall awareness and knowledge about the TTS risk among the public

While many participants reported to be very aware about TTS and its association with Vaxzevria and Jcovden, many were not familiar with its symptoms. Most survey respondents reported to have become aware of TTS in the second quarter of 2021, between April and May.

Despite that, for the majority, the information about these side effects negatively affected their wish to be vaccinated with Vaxzevria or Jcovden.

1.9.9 Sources of information about TTS risk among the public

The main source of information about COVID-19 vaccines' risks and benefits, including information about TTS, was mainstream media, i.e., televised press conferences held by authorities, which were also referred to by the HCP and experts during the interviews. Internet and social media also seemed to have played a vital role, whereas healthcare professionals had a modest contribution.

1.9.10 Citizens' attitudes towards vaccination against SARS-CoV-2

The overwhelming majority of survey respondents were vaccinated against COVID-19, with the highest reported coverage in Portugal, where only 4.5% had not received a vaccine. In contrast in Latvia, approximately 43.7% were not vaccinated.

The main reasons to get vaccinated were to avoid becoming ill, protecting family and friends, and preventing spread of COVID-19 in society. In contrast, main reasons not to get vaccinated were concerns about the vaccine's side effects and that COVID-19 vaccines had not been sufficiently tested; the push from authorities towards vaccination, and a preference to develop immunity naturally.

Generally, the attitudes towards vaccination, including towards COVID-19 vaccines, were more positive than negative, apart from Latvia. Overall, respondents viewed the widespread use of vaccines to prevent disease more positively than the use of vaccines against COVID-19, which were perceived more negatively. This was particularly true when considering the safety of the COVID-19 vaccines.

Citizens were asked to score what their perceptions were of the vaccines at the time of approval ranging from 1 (mainly disadvantages) to 10 (mainly advantages). Jcovden was attributed overall a lower score than other COVID-19 vaccines, including Vaxzevria. This might be explained by its relatively low use across the countries included in our study or by a higher awareness of associated TTS risk with Jcovden among respondents, given that it entered the market at later stage.

1.9.11 Impact of changes to national vaccination campaigns or reports about TTS on the public

Among those respondents who reported to have changed their willingness to be vaccinated with Vaxzevria or Jcovden, most conceded to be less willing to receive these vaccines. This negative effect was slightly more visible when respondents were asked about the impact of the TTS reports.

1.10 Discussion

Our results clearly show that changes occurred in vaccination policies over time, which were sequential to the EMA Risk Communication. However, we cannot ascertain the real impact of the EMA risk communication, as policy changes might also have been the result of an ever-dynamic combination of factors: increasing evidence about associated TTS risk, available COVID-19 vaccines, national political agendas as well as media/public pressure to respond promptly to safety concerns while not jeopardizing ongoing national vaccination campaigns.

The greater variation across countries for the vaccination policies concerning Jcovden could be due to the vaccine's availability, or its targeted use for specific population groups which varied greatly across the countries included in the study. For instance, Portugal and Greece had access to this product at a later stage than Denmark or the Netherlands. The working mechanism of these vaccines was already known by the time Jcovden entered the market, whereas Vaxzevria was the first of its kind and any new safety information was more likely to result in changes to the product information and subsequently to vaccination practices, resulting in more harmonized changes across the EU. In Greece Jcovden was used to vaccinate specific target groups, based on their geographic location, age and mobility.

The decision to suspend the use of Vaxzevria and Jcovden in Denmark from the national vaccination programme was based on the results of an epidemiological study and the assessment of vaccination coverage at that time. The study, conducted in national registers in Denmark and Norway, provided evidence of a causal relation between the use of these vaccines and TTS, on occasions with fatal outcomes.

Although in many countries the vaccination advisory committees followed the recommendations of the EMA, these were not always implemented in the national policies. The decisions were often affected by the availability of the vaccine or by other political influences.

An overwhelming majority of healthcare professionals were aware about the reports of TTS associated with COVID-19 adenovirus vector vaccines. Half of respondents were able to identify the correct risk of developing TTS (i.e., very rare side effect).

The knowledge about TTS risk has evolved over time. Initially, more cases were identified in females under 60, possibly due to the rollout of vaccines among certain target groups. Whilst the EMA concluded that no risk factors were clearly identified, initial reports by the media and experts played a key role in the decisions around the national vaccination policy changes. Our survey results show that there seems to still be a belief among HCPs that TTS is more prevalent among females or that specific age groups are at higher risk. This might be a testament of the role played by the media when relaying the initial information. They played a more salient role in shaping beliefs and knowledge about vaccines benefits and risks than the EMA's scientific communications.

We would expect that healthcare professionals would be capable of identifying all TTS symptoms and likely outcomes, both major and minor. Our results showed that while they could identify key symptoms and fatal /serious outcomes, they failed to detect both minor symptoms and non-serious effects from a list. We consider this to be a gap in knowledge, which might be the result of ample media coverage of TTS, where more fatal and serious events and outcomes were featured prominently. In countries where the respondent population was younger, internet and social media were valuable information sources on TTS risk. Notwithstanding, healthcare professionals still reported relying on guidelines from authorities, expert opinions from peers or guidelines from learned societies, when available.

Among the public, the overall awareness about TTS risk associated with Vaxzevria and Jcovden was high, but hardly any respondents were familiar with its symptoms. Here, mainstream and social media seemed to have played a leading role in the dissemination of information about COVID-19 vaccines' risks. While generally attitudes towards the use of vaccines to prevent disease remained positive, some respondents admitted that the reports about these side effects negatively affected their wish to be vaccinated with Vaxzevria or Jcovden. These findings further underscore how paramount the communication of risk can become in dynamic and evolving circumstances, such as that of the pandemic.

Considering the importance granted by patients and healthcare professionals to the role played by mainstream media in the dissemination about risks and benefits from COVID-19 vaccination, it might be pertinent to explore how risk communication from the EMA can be further adapted to increase the opportunities to communicate with the public about risks, particularly when addressing uncertainties. This might involve a stepwise approach towards risk communication, whereby healthcare professionals would receive the information promptly prior to the media, but under embargo. The addition of figures and other infographics into EMA risk communication to inform both professionals and the public would be helpful. Such figures have shown impact in other fields

but should be used carefully and targeted towards the target groups. Also, our results show that the materials are more likely to be used when easily retrievable and accessible online.

The role played by the information provided by the EMA/Drug Regulatory Agencies (DRA) seemed relatively modest, particularly in relation to guidelines from health authorities, which are recognized as having the greatest impact on professional practice. There was moderate to high awareness about the regulatory measures established by the EMA in 2021, for healthcare professionals, with variability across countries. The SmPC and the package leaflet were not amply used, with some exceptions. In contrast the DHPC did seem to permeate more healthcare professionals across all countries. Yet there were still health professionals who did not know these documents exist or have ever used them.

Healthcare professionals reported to be more alert about monitoring health symptoms after vaccination, following the TTS risk minimisation recommendations. This also involved proactively informing citizens about TTS symptoms and about the need to seek further assistance should warning signs occur. While these results are encouraging, they should be interpreted with caution as we have also clearly proven gaps exist in the recognition of symptoms by healthcare professionals.

1.11 Conclusion

This study aimed to assess the impact of the regulatory actions for Vaxzevria and for Jcovden following the 2021 safety review. We observed a great variability across countries as to the implementation of their vaccination policies and subsequent changes. However, we cannot ascertain the real impact of the EMA risk communication, as policy changes might also have been the result of a combination of factors: increasing evidence about associated TTS Risk, national political agendas as well as media/public pressure to respond promptly to safety concerns while not jeopardizing ongoing national vaccination campaigns.

Our study showed that the awareness about the TTS risk of adenoviral vector vaccines was high among the public and healthcare professionals across the six countries surveyed.

Our outcomes from the healthcare professionals' surveys indicated that while awareness about the risk of TTS was extremely high among healthcare professionals across the countries studied, some gaps existed in their knowledge as to its signs and symptoms and particularly as to its likely outcomes and perceptions of risks groups.

Healthcare professionals reported a clear preference for national guidelines, with the actual use of the EMA information remaining relatively moderate across countries, with some variations. There was moderate to high awareness about the regulatory measures established by the EMA in 2021, for healthcare professionals, with variability across countries.

Our study found that the public respondents were aware about TTS but had limited knowledge about its signs and symptoms. Across most countries, attitudes towards COVID-19 vaccination remained more positive than negative, yet perceptions towards the safety of COVID-19 vaccines have been altered, most likely due to the reports of TTS than to the changes to the vaccination policies.

1.12 Marketing authorisation holder

This study focused on the risk awareness with respect to two SARS-CoV-2 adenovirus vector vaccines for active immunisation against COVID-19 (see Table 4). This study was initiated and funded by EMA under procurement procedure EMA/2017/09/PE (Lot 3). Both vaccines received a conditional marketing authorisation in the European Union in 2021. The marketing authorisation holders were not involved in this study.

Table 4. Vaccines included in the study

Product name	Agency Product Number	Marketing-authorisation holder	INN Active ingredient	ATC-code
Vaxzevria (previously COVID-19 Vaccine AstraZeneca)	EMEA/H/C/005675	AstraZeneca AB	COVID-19 Vaccine (ChAdOx1-S [recombinant])	J07BX03
Jcovden (previously COVID-19 Vaccine Janssen)	EMEA/H/C/005737	Janssen-Cilag International NV	COVID-19 vaccine (Ad26.COV2-S [recombinant])	J07BX03

2 Investigators

Table 5 provides an overview of the principal investigators in this study. More details about the investigators and the tasks and structure of the various teams (Coordination, National and Steering) are available under Annexes 1 and 2, respectively.

Table 5. Names and affiliations of principal investigators

Name	Role	Country
Prof. Olaf Klungel, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands	Consortium Director	The Netherlands
Dr Teresa Leonardo Alves, Centre for Health Protection (GZB), National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands	Principal Investigator Study Coordinator Coordinating Team Member	The Netherlands
Prof. Anna Birna Almarsdóttir, Professor, Social and Clinical Pharmacy, Department of Pharmacy, Faculty of Health and Medical Sciences, University of Copenhagen	Lead Investigator Denmark Steering Committee Coordinating Team Member	Denmark
Dr Christos Kontogiorgis, Assistant Professor, Laboratory of Hygiene and Environmental Protection, Faculty of Medicine, School of Health Sciences, Democritus University of Thrace, Alexandroupolis, Greece	Lead Investigator Greece Steering Committee	Greece
Dr Elita Poplavska, Assistant Professor, Faculty of Pharmacy & Institute of Public Health, Riga Stradins University, Riga, Latvia	Lead Investigator Latvia Steering Committee	Latvia
Dr Ingrid Hegger, Expert Researcher, Centre for Health Protection (GZB), National Institute for Public Health, and the Environment (RIVM), Bilthoven, the Netherlands	Lead Investigator Netherlands Steering Committee Coordinating Team Member	The Netherlands
Ella van Vliet, M.Sc., researcher, the Centre for Health Protection (GZB), National Institute for Public Health, and the Environment (RIVM), Bilthoven, the Netherlands	Lead Investigator Netherlands (from March 2022 onwards) Coordinating Team Member	The Netherlands
Joëlle Hoebert, PhD, researcher, Centre for Health Protection (GZB), National Institute for Public Health, and the Environment (RIVM), Bilthoven, the Netherlands.	Investigator Netherlands	The Netherlands
Adrie de Bruijn, M.Sc., researcher, Centre for Health Protection (GZB), National Institute for Public Health, and the Environment (RIVM), Bilthoven, the Netherlands.	Investigator Netherlands	The Netherlands
Dr Inês Ribeiro Vaz, Faculty of Medicine, University of Porto, Portugal	Lead Investigator Portugal Steering Committee	Portugal
Prof. Mitja Kos, MPharm, University of Ljubljana, Faculty of pharmacy, Department of Social Pharmacy, Ljubljana, Slovenia	Lead Investigator Slovenia Steering Committee	Slovenia
Dr E.R. (Rob) Heerdink, Associate professor of Clinical	Advisor	Netherlands

Pharmacoepidemiology, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University.	Coordinating Team Member	
Dr Shahab Abtahi, MD PhD, Postdoctoral Researcher, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University	Advisor Coordinating Team Member	Netherlands
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