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Safety monitoring of COVID-19 vaccines: perspective from the European Medicines Agency

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ABSTRACT

Prior to deployment of COVID-19 vaccines in the European Union (EU) in 2021, a high vaccine uptake leading to an unprecedented volume of safety data from spontaneous reports and real-world evidence, was anticipated. The European Medicines Agency (EMA) implemented specific activities to ensure enhanced monitoring of emerging vaccine safety information, including intensive monitoring of reports of adverse events of special interest (AESIs) and the use of observed-to-expected (O/E) analyses. EMA also commissioned several independent observational studies using a large network of electronic healthcare databases and primary data collection via mobile and web-based applications. This preparedness was key for two high-profile safety signals: thrombosis with thrombocytopenia syndrome (TTS), a new clinical entity associated with adenovirus-vectored vaccines, and myocarditis/pericarditis with messenger RNA (mRNA) vaccines. With no existing case definition nor background rates, the signal of TTS posed particular challenges. Nevertheless, it was rapidly identified, evaluated, contextualised and the risk minimised thanks to close surveillance and an efficient use of available evidence, clinical expertise and flexible regulatory tools. The two signals illustrated the complementarity between spontaneous and real-world data, the former enabling rapid risk identification and communication, the latter enabling further characterisation. The COVID-19 pandemic has tremendously enhanced the development of tools and methods to harness the unprecedented volume of safety data generated for the vaccines. Areas for further improvement include the need for better and harmonised data collection across Member States (e.g., stratified vaccine exposure) to support signal evaluation in all population groups, risk contextualisation and safety communication.

INTRODUCTION

After emerging in late 2019 in Wuhan, China, the SARS-CoV-2 virus rapidly turned into a global pandemic with devastating morbidity and mortality. Safe and effective vaccines were urgently needed to control the public health impact of COVID-19 and allow societies to re-open. COVID-19 vaccines were developed at unprecedented speed and approved in an accelerated manner by many regulatory authorities. In the European Union (EU), COVID-19 vaccines were authorised following a 'rolling review', a regulatory tool used by the European Medicines Agency (EMA) to speed up the assessment of promising medicines during public health emergencies without compromising quality, efficacy and safety [1]. By March 2021, a year after the World Health Organization (WHO) officially declared COVID-19 a pandemic, four COVID-19 vaccines had received a centralised conditional marketing authorisation in the EU. An overview of the vaccines is provided in Table 1.

Prior to the approval of COVID-19 vaccines, it was anticipated that the mass vaccination campaigns required to control the pandemic would result in an unprecedented volume of safety data from spontaneous reporting systems, the scientific literature and pharmacoepidemiological studies. Moreover, many vaccine candidates were based on innovative platforms, such as messenger RNA (mRNA) or viral vectors. Except for two recent Ebola vaccines based on viral vectors with limited patient exposure [2, 3], such vaccines had not been previously authorised, and thus did not have

established post-marketing safety profiles. The rapid detection, prioritisation, assessment, communication and management of emerging safety information that may impact the benefit-risk of the vaccines once deployed were therefore essential to guide vaccination policy makers and maintain public confidence in the vaccines. These EU preparedness activities were outlined in a specific pharmacovigilance plan, which built on the experience gained during the 2009 H1N1 influenza pandemic while taking into account COVID-19 specificities [4].

A list of adverse events of special interest (AESIs) i.e., adverse events to closely monitor during and after the development of COVID-19 vaccines, was proposed by the Brighton Collaboration within the Safety Platform for Emergency vACcines (SPEAC) [5]. While AESIs are essential to focus monitoring efforts, the occurrence of serious unpredictable safety issues, particularly in a mass vaccination context, remains a top-of-mind concern for regulators. A notable example is the risk of narcolepsy with the adjuvanted 2009 H1N1 pandemic influenza vaccine Pandemrix [6]. The pathogenesis is still not fully elucidated, with several hypotheses including the role of a wild-type virus infection through a multifactorial mechanism involving antigen mimicry [7, 8]. Narcolepsy was not on the AESI list for H1N1 pandemic vaccines as it had not been causally associated with any vaccine before [9].

In this paper, we provide an overview of the main tools implemented by EMA to monitor emerging safety information on COVID-19 vaccines approved in the EU, with an emphasis on EudraVigilance data and real-world evidence from observational studies. We describe how these tools were mobilised for two high-profile signals: thrombosis with thrombocytopenia syndrome (TTS) with adenovirus vaccines (initially Vaxzevria), and myocarditis/pericarditis with mRNA vaccines (Comirnaty and Spikevax) (Table 2). Both signals were associated with challenges and achievements, which are a valuable source of lessons for the continued monitoring of COVID-19 vaccines and future pandemic preparedness.

MONITORING TOOLKIT

Enhanced monitoring of case reports in EudraVigilance

A signal is information on a new potentially causal association, or a new aspect of a known association, between a drug and an event that requires further investigation [10]. In a mass vaccination programme which involves large exposure over a relatively short time period, signal detection should be conducted in real-time, where feasible [11].

EudraVigilance is the system for collecting, managing and analysing suspected adverse reactions to medicines authorised in the European Economic Area (EEA) [12]. According to EU legislation, serious individual case safety reports should be submitted to EudraVigilance by national competent authorities of EU Member States or marketing authorisation holders within 15 calendar days [13]. A shorter timeframe was encouraged whenever feasible for case reports with COVID-19 vaccines containing AESIs, or fatal or life-threatening events [4]. Emphasis was also placed on the quality of information in case reports which is important for causality assessment.

Signal detection in EudraVigilance is based on an integrated approach that combines: 1) quantitative aspects using the reporting odds ratio as measure of disproportionality together with defined thresholds for case counts, 2) clinical considerations that take account of fatal, important or designated medical events [14]. This approach is implemented in periodic monitoring reports that provide summarised information on case reports received for a drug of interest and are used by EMA and Member States to perform routine signal detection in EudraVigilance. The standard monitoring periodicity for newly authorised medicines is fortnightly, but for COVID-19 vaccines, monitoring reports were initially screened weekly (Figure S1).

To ensure an enhanced monitoring of AESIs, we developed a list of targeted medical events for vaccines. The list was largely based on the AESI list developed by SPEAC on the basis of proven associations with immunisation, theoretical concerns linked to immunopathogenesis, non-clinical data or the SARS-CoV-2 infection itself [5]. We however introduced some adaptations mainly driven by feasibility, having in mind that causality is more readily assessed via spontaneous reports for certain events, while active surveillance is more appropriate for others. The targeted event list consists of a mapping of selected AESIs to preferred terms (PTs) of the Medical Dictionary for Regulatory Activities (MedDRA) (Table S1). The list is refined regularly based on experience. In early stages of vaccine deployment, case reports containing targeted events are reviewed in an almost 'real-time' manner using a case review tracking system, until there is enough evidence for escalation (e.g., raising a signal), or until the volume of reports makes alternative approaches more appropriate (e.g., review of aggregated data via monitoring reports).

Observed-to-expected analyses

O/E analyses compare the number of 'observed' cases of an event in vaccinees recorded in a data collection system, to the number of 'expected' cases, i.e. those that would have naturally occurred in the same population without vaccination, estimated from background incidence rates [15].

In O/E analyses conducted by EMA, 'observed' cases are based on spontaneous reports in EudraVigilance from the EEA. Risk periods are generally determined based on published case definitions, biological plausibility (e.g., 42 days for Guillain-Barre syndrome [16]) or time-to-onset distribution. COVID-19 vaccine exposure data required to calculate the number of 'expected' cases is extracted from the European Centre for Disease Prevention and Control (ECDC) website [17]. As ECDC data are not stratified by age and gender for all countries, further processing is performed by EMA using stratified distribution data actively obtained from a subset of Member States, assuming a similar vaccine distribution across countries. Background incidence rates for AESIs were generated by the ACCESS project (vACCine covid-19 monitoring readinESS). ACCESS was launched by EMA in April 2020 and coordinated by University Medical Center (UMC) Utrecht with the Vaccine monitoring Collaboration for Europe (VAC4EU) [18]. The first set of background rates was made available mid-December 2020, in time for the authorisation of the first COVID-19 vaccine in the EU [19]. For events not addressed in ACCESS data (e.g., non-AESIs) or requiring further refinement, background rates are ascertained from healthcare databases EMA has access to.

Observed-to-expected (O/E) analysis is a useful quantitative signal detection tool for vaccines, particularly during mass vaccination, yet it is not intended to prove or exclude a causal association [11]. O/E analyses are subject to caveats and limitations that should be considered when interpreting their results. *1) Comparability.* Expected and observed cases are ascertained from data sources with different characteristics, including coding dictionaries and diagnostic criteria. An important preliminary step to O/E analyses involves a careful mapping between MedDRA terms for the 'observed' cases and the International Classification of Diseases (ICD) codes generally used in healthcare databases. A poor alignment between the codes may affect the validity and interpretability of the O/E results. *2) Representativeness.* Background rates are ascertained from national databases that may not be fully representative of the entire EEA. Besides, there can be substantial heterogeneity when background rates are available from multiple databases. The background population may also differ from the exposed population, when certain at-risk groups are prioritised for vaccination. *3) Underestimation of the observed cases.* There may be under-reporting of some events, or delayed reporting, especially in a health crisis context where backlog may occur. *4) Overestimation of the observed cases*. Some events may be more intensively diagnosed and reported in vaccinees ('observed') than in routine clinical practice ('expected'). Sensitivity analyses are performed, when relevant, to mitigate these limitations and other uncertainties (e.g., diagnostic certainty, time-to-onset). Despite their caveats,

O/E analyses, particularly when stratified by age and gender, have provided additional evidence on the safety profile of each COVID-19 vaccine.

Reporting rates

Reporting rates are a simple and useful tool to contextualise events by giving a sense of their magnitude. We have used crude reporting rates to view trends over time in order to explore the impact of regulatory actions as well as differences within each vaccine between doses, gender or age groups. Reporting rates also have limitations. For example, they do not account for the time the vaccinated population is at risk of the event, or differences in vaccination schedules (e.g., demographics change at different stages of the vaccination campaign). Public awareness may also favour certain reports in some periods and impact reporting rates.

Observational studies

Post-authorisation safety studies conducted by vaccine manufacturers are described in the risk management plans, which are published on the EMA website for COVID-19 vaccines. In addition, independent observational studies were commissioned by EMA (Figure 1). In January 2020, EMA launched an early hypothesis-generating, active surveillance study to monitor the first vaccinations [20, 21]. It included primary data collection in seven countries and parallel cohort monitoring of AESIs and COVID-19 diagnoses before and after vaccination in large healthcare databases. The study provided a framework for further readiness and generation of new background rates and pharmacoepidemiological analyses. This first early study transitioned into a larger study, including a monitoring of special populations in the primary data collection part (e.g., pregnant women, immunocompromised populations), while the secondary data component reinforces the framework to promptly address emerging safety concerns [22, 23]. Of note, children and adolescents are included in the prospective component of the larger study as well as dedicated EMA-funded safety studies. EMA also procured multinational etiological studies to further address emerging safety concerns, such as TTS. Finally, international studies were initiated through collaborations with the United States' (US) Food and Drug Administration (FDA) and other regulators such as Health Canada.

CASE STUDIES

Thrombosis with thrombocytopenia syndrome

On 7 March 2021, the Austrian Agency for Health and Food Safety (AGES) alerted the EU regulatory network to unusual cases of thromboembolic events, one of which was fatal, following administration of Vaxzevria, and suspended the use of a specific batch of the vaccine. Over the following days more Member States paused vaccination with certain batches of Vaxzevria or with the vaccine altogether. On 9 March 2021, based on a preliminary assessment by EMA's Pharmacovigilance Risk Assessment Committee (PRAC) and Biologics Working Party, a batch-specific issue was considered unlikely. A broader evaluation of thromboembolic events by PRAC was initiated, including EudraVigilance, quality, clinical, pre-clinical and literature data, which led to the identification of a new risk possibly linked to Vaxzevria: a rare combination of thrombosis with thrombocytopenia [24]. By 24 March 2021, the product information was updated and healthcare professionals and the public were warned about the risk [25]. An independent expert meeting was convened on 29 March 2021, gathering experts in haematology, neurology, cardiology, infectiology, immunology, virology and epidemiology from all over Europe. A causal association between Vaxzevria and TTS was considered plausible from that point on [26]. To better inform national vaccination campaigns, the European Commission requested under Article 5(3) of Regulation (EC) No 726/2004 [27], that EMA's Committee for Medicinal Products for Human Use (CHMP) review available data to further characterise the risks and benefits of Vaxzevria in different populations, identify possible risk factors and provide a recommendation regarding a second

dose. This exercise revealed that the benefits of Vaxzevria increased with age and infection rates. There was not enough evidence to contextualise the risk according to sex, nor to change the existing recommendation regarding a second dose [28, 29]. These regulatory steps are summarised in Figure S2.

TTS presents similar clinical and serological features to heparin-induced thrombocytopenia. Both syndromes are associated with high-titre immunoglobulin G class antibodies directed against the cationic platelet chemokine, platelet factor 4 (PF4) [30]. These antibodies activate platelets leading to platelet consumption and thromboembolic complications. TTS can manifest as venous thrombosis, often in unusual locations such as the cerebral or abdominal veins, as well as arterial thrombosis, concomitant with thrombocytopenia. The term 'thrombosis with thrombocytopenia syndrome' was proposed by the Brighton Collaboration for case finding [31] and has generally been adopted by regulators around the world to designate the adverse reaction to adenovirus-based COVID-19 vaccines. 'Vaccine-induced thrombotic thrombocytopenia' (VITT), which designates the same syndrome but implies a causal association with vaccination and the involvement of anti-PF4 antibodies, seems preferred by clinical researchers. Strictly-speaking, coincidental thrombosis and thrombocytopenia can occur in clinical contexts other than post-vaccination, for instance in cancer or thrombotic thrombocytopenic purpura [32].

In the months that followed the emergence of the signal, several case definitions of TTS were developed by regulators and researchers. The working definition used by the US Centers for Disease Control and Prevention (CDC) comprised two tiers based on the location of thrombosis (unusual or common) and the presence or absence of anti-PF4 antibodies [33]. A panel of British haematologists defined VITT cases according to five criteria considering time-to-onset, thrombosis, thrombocytopenia, D-dimer levels, and anti-PF4 antibodies. Cases are classified as definite, probable, possible or unlikely depending on the criteria met [34]. The Brighton Collaboration's interim definition was less specific as anti-PF4 antibodies were not required at any level [31].

When the signal of TTS emerged, there were no case definition, background incidence rates or specific MedDRA terms[1]. Early O/E analyses were based on background rates using proxies such as coagulation disorders, disseminated intravascular coagulation and cerebral venous sinus thrombosis (CVST), regardless of thrombocytopenia. These rates were calculated by ACCESS using two databases (ARS Tuscany for Italy and FISABIO for Spain) [18]. Observed cases were EudraVigilance reports of thromboembolic events (Standardised MedDRA query [SMQ] 'Embolic and thrombotic events'), disseminated intravascular coagulation and CVST, respectively. The number of observed cases of CVST was higher than expected, especially in the younger age groups. This imbalance persisted when observed cases of CVST were stratified according to the presence or absence of thrombocytopenia (Figure 2). Of note, CVST without thrombocytopenia was later added to Vaxzevria's product information [35]. For disseminated intravascular coagulation and thromboembolic events in general the observed number of cases was lower than expected, except in the younger age groups [24]. In cases of thrombosis with thrombocytopenia reported to EudraVigilance, there was a female predominance. This was reflected in the initial warning on TTS included in Vaxzevria's product information. Vaccine exposure data stratified by gender were actively sought from Member States to support the contextualisation exercise. However, few countries were able to provide such information, thus the analyses could not conclude on whether or not sex was a risk factor for TTS [28]. The reference to women was later removed from the product information based on further evidence [34, 36]. Jcovden had not been deployed in the EU when the first TTS cases were reported in the US. The evaluation of available evidence by PRAC led to regulatory actions similar to those taken for Vaxzevria [37].

[1] Thrombosis with thrombocytopenia syndrome was added to MedDRA in September 2021.

Since the TTS signal emerged, a 'proxy' approach has been used to retrieve potential cases from EudraVigilance, based on the co-reporting of at least one PT from the MedDRA SMQ 'Embolic and thrombotic events' and one MedDRA PT suggestive of thrombocytopenia in the reaction field (Table S2). Other fields such as case narrative or test results are not routinely screened during case retrieval. A manual case adjudication by EMA clinical experts was performed in the early stages of signal evaluation, until no longer feasible due to scalability issues. The 'proxy' strategy has specificity and sensitivity issues. On one hand, a non-negligeable proportion of retrieved cases - up to 30 or 40% based on experience from routine pharmacovigilance procedures - do not meet TTS criteria upon further scrutiny. On the other hand, actual TTS cases may be missed, if, for instance no thrombocytopenia-related term is coded as a reaction, or if the case represents a less typical presentation of TTS, e.g. with normal platelet count [38]. The inclusion of a specific term for TTS in MedDRA was essential, but only applicable to prospective cases.

Despite their limitations, analyses of EudraVigilance data were key to the evaluation and characterisation of the signal. EudraVigilance has also been used by independent research teams working on TTS. One team showed that the fatality rate of cases of CVST with thrombocytopenia reported to EudraVigilance after vaccination with the adenoviral vector-based vaccines had significantly decreased over time, suggesting a beneficial effect of earlier recognition and/or improved management of the condition [39].

EMA-funded studies relevant to TTS are summarised in Table 3. A cohort study on the association between TTS or venous or arterial thromboembolic events and COVID-19 vaccines, was commissioned by EMA in summer 2021 and conducted by a consortium led by Erasmus and Oxford universities using several large healthcare databases. The evaluation of the risk of TTS or thromboembolism in vaccinated vs. unvaccinated subjects was limited by confounding by indication due to differences in vaccine uptake and prioritisation of specific subgroups for earlier vaccination. Comparative analyses showed a 30% increased risk of thrombocytopenia following 1-dose Vaxzevria (vs 1-dose Comirnaty), a potential double risk of TTS-venous thromboembolism following Jcovden (vs 1-dose Comirnaty), and a possible 2-to-4-fold increased relative risk of CVST following Jcovden or Vaxzevria. However, anti-PF4 measurement could not be ascertained from the data, and the study was underpowered for rare events like CVST. Post-vaccine thromboembolism and TTS were observed more commonly amongst elderly men with specific comorbidities and medicines use, in contrast with spontaneous reports of TTS/CVST, which appeared to affect predominantly younger women. Also, heparin was frequently used to manage post-vaccine TTS, which suggests that some cases may not represent true VITT since early clinical guidelines warned against its use. Finally, the genetic determinants of post-vaccination venous thromboembolism were consistent with historical data, suggesting a similar aetiology [40, 41].

Studies on the natural history of coagulopathy and use of anti-thrombotic agents in COVID-19 patients were initiated by the FDA and EMA using a joint protocol [42]. The study in Europe, led by the universities of Erasmus and Oxford, started in Spring 2020; when the TTS signal emerged, a cohort of vaccinated subjects was added. The study estimated the incidence rates of coagulopathies and TTS in four cohorts using databases in two countries: the general population in the pre-pandemic period; unvaccinated individuals with a recent COVID-19 infection; individuals with a first dose of Vaxzevria or Comirnaty. Pre-pandemic background rates, although very low, were higher among older and male individuals and those with more comorbidities and greater medication uptake [43, 44, 45].

To evaluate the impact of regulatory actions and communications concerning TTS for Vaxzevria and Jcovden, a study was set up in late 2021. The study aims at assessing levels of awareness and changes in attitude amongst healthcare professionals as well as modifications of national vaccination policies in six Member States [46].

Myocarditis and pericarditis

Myocarditis and pericarditis have been reported in association with COVID-19 infection and were therefore included in the AESI list developed by SPEAC [5]. In early 2021, a signal of myocarditis emerged in Israel for Comirnaty. Most cases were mild and resolved within a few days. They occurred predominantly in young (16-19 years) male vaccinees after the second dose. This triggered a review of myocarditis and pericarditis for both mRNA vaccines at EU level.

As of May 2021, 145 cases of myocarditis had been reported to EudraVigilance from EEA countries for Comirnaty. Cases were assessed against the Brighton Collaboration's criteria [47], with 66 meeting levels 1-3 of the case definition. A third of these cases occurred after the first dose, a third after the second dose, while dose information was missing from the remaining cases. Cases in vaccinees 30 years and younger showed a predominance in males following the second dose. In the majority of cases (99), there were no reported alternative aetiologies or confounders. Together with the temporal association (median time-to-onset: 8 days), this suggested a possible causal association with the vaccine. The evidence from cases of pericarditis was somewhat weaker, a causal relationship could not be excluded [48]. For Spikevax, the exposure was lower than for Comirnaty and there were fewer cases of myocarditis and pericarditis in EudraVigilance by the end of May 2021, but a more than 2-fold increase was observed in the following 3 weeks, which may have been stimulated by media attention [49]. For O/E analyses of myocarditis, background rates were calculated by ACCESS on the ARS (Tuscany) database [18]. Observed cases were retrieved using the MedDRA High Level Terms (HLTs) 'Infectious myocarditis' and 'Noninfectious myocarditis (incl. myopericarditis)'. Exposure data stratified by age and gender were sourced from ECDC and directly from Member States. O/E ratios were statistically significant in 18-24 year old males for both vaccines. O/E ratios were generally lower in the older age groups and in females (Figure 3). The occurrence of cases of myocarditis and pericarditis was reflected in the product information of the two vaccines and communicated to healthcare professionals and the public [50].

In the months that followed, two large European pharmacoepidemiological studies including paediatric individuals provided further evidence on the risk of myocarditis and pericarditis following administration of mRNA vaccines: a cohort study based on Nordic registry data, and a case-control study based on the French national health data system [51, 52]. The two studies provided estimates of the number of excess cases of myocarditis after the second dose of mRNA vaccine in young vaccinees compared to unexposed: 0.26 (French data) and 0.57 (Nordic data) per 10,000 for Comirnaty, 1.3 and 1.9 per 10,000, respectively, for Spikevax. These findings were reflected in the product information [53, 54]. The signal was also addressed using the framework coordinated by UMC Utrecht and VAC4EU: a pharmacoepidemiological study was conducted using large healthcare data from four countries, with two study designs. The results confirmed the findings from the French and Nordic countries and also showed that COVID-19 disease itself increased the incidence rates of these events [53].

LESSONS LEARNED

On facing a massive influx of spontaneous reports

Due to the nature of the COVID-19 pandemic, the uptake of the vaccines and thus the reporting of suspected adverse reactions had been anticipated to be very high, much higher than for the 2009 A/H1N1 pandemic. This prediction was confirmed: within 3 months of the start of the deployment of COVID-19 vaccines in the EEA, the total number of reports for these vaccines in EudraVigilance was almost 20 times that of H1N1 pandemic vaccines in the same timeframe (Figure S3). While reporting levels for H1N1 vaccines reached a plateau after a few months [55], for COVID-19 vaccines they have continued to grow steadily. As of June 2022, nearly two million reports (14% of all reports) in EudraVigilance were related to COVID-19 vaccines, with Comirnaty accounting for over one million

reports. This unprecedented volume is largely explained by the size of the vaccination campaigns (Table 1), the reporting tools in place in EU Member States and increased communication to encourage reporting of adverse events.

Spontaneous data are a highly valuable and effective source of early information on adverse reactions. In both signals discussed in this paper, EudraVigilance data allowed to rapidly characterise and communicate about the risks, before real-world evidence could be generated. O/E analyses, in particular, have helped contextualise suspected adverse reaction reports and minimise the biases inherent to spontaneous reporting.

However, such levels of reporting come with challenges. *1) Quality of case documentation.* The prioritisation and streamlining required amongst vaccine manufacturers and Member States to process the high volumes of reports had an unavoidable impact on the completeness of information. *2) Scalability of manual reviews.* Individual case review is a key activity during traditional signal validation, but a systematic review is hardly feasible beyond a certain number of reports. *3) Methodological impact.* The large contribution of certain COVID-19 vaccines to reports in EudraVigilance has an impact on reporting odds ratios for other COVID-19 vaccines and other medicines, with signals being masked or false associations being flagged as potential signals. Interestingly, in the US Vaccine Adverse Event Reporting System (VAERS), masking has been found to be rare overall, but more likely to affect COVID-19 vaccines than other vaccines, and regression-based methodologies may help address the problem [56].

On generating near real-time, real-world evidence

The ACCESS framework and the readiness of other organisations collaborating with EMA allowed to rapidly generate or update case definitions and provide background rates, while monitoring via the early safety study showed that large-scale, prospective surveillance is feasible. Prospective data collection complemented routine pharmacovigilance by providing insights on the denominator for spontaneous reports and generating incidence rates for many events, including AESIs, but also highlighted operational limitations due to heterogeneity in vaccination rollout. Transitioning from early to continued readiness, a consolidated framework is in place to generate valid evidence on the signals through dedicated safety studies.

On dealing with incomplete information

Missing information is usually mitigated with workarounds, assumptions and imputations as appropriate, but ideally, efforts should be concentrated on addressing the issues at their source. *1) Appropriately stratified exposure data* should be routinely collected by all EEA countries and centralised by ECDC. Such strata include age, gender, vaccine brand and dose and special populations (e.g. pregnant women). *2) Expedited reporting timelines to EudraVigilance should be shortened* to a few days when feasible to support a prompt assessment of urgent signals. *3) A standardised structured way of reporting dose* information in case reports should be enforced to facilitate analyses by dose. *4) Recent healthcare database data on clinical outcomes and covariates* linked at individual patient level, and at different levels of healthcare (primary and secondary) are needed to timely address emerging safety concerns.

Estimating the extent of under-reporting in EudraVigilance remains a challenge as it may be influenced by numerous factors including public awareness, seriousness, demographics or local practices. In the contextualisation exercise for TTS, under-reporting levels were assumed as follows in the sensitivity analysis: 0% in the first 7 days post-vaccination, 20% between day 8 and day 14, 50% after day 14 [28]. Higher degrees of under-reporting (30%, 50%, 80%) were applied in the sensitivity analyses performed for myocarditis (data not shown).

On capitalising on a challenging signal

As a new clinical entity with no case definition or background incidence rates, the signal of TTS with Vaxzevria posed multiple challenges. Yet, thanks to the mobilisation of an impressive amount of resources and expertise throughout Europe, and the use of available scientific and regulatory tools in an efficient and flexible manner, the signal was identified, assessed, characterised and communicated within a few weeks, resulting in the implementation of risk minimisation measures.

The scientific knowledge and regulatory experience acquired with Vaxzevria proved useful when TTS cases emerged with Jcovden in the US, allowing the risk to be added to the product information before Jcovden was deployed in the EU. More generally, TTS acted as a 'baptism by fire' in the safety monitoring of COVID-19 vaccines and increased the readiness to subsequent signals.

The contextualisation of a risk with the benefit of a vaccine in different populations and epidemic scenarios done for Vaxzevria and TTS is rarely performed in a regulatory context. This holistic approach may be useful in other situations, with a quantitative benefit/risk assessment that would account for changes in the epidemiologic situation, effectiveness and safety over time.

The TTS signal also highlighted the need for more research on signal detection methods aimed at identifying from spontaneous reporting systems groups of case reports that may point to new or poorly characterised syndromes, for example cluster analyses [57].

On working collaboratively

There have been unprecedented cooperation and coordination with other regulators and organisations, including CDC, ECDC, FDA, Health Canada, the UK Medicines and Healthcare products Regulatory Agency (MHRA), National Immunization Technical Advisory Groups (NITAGs), the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), WHO, as well as independent researchers and experts. Notably, the International Coalition of Medicines Regulatory Authorities (ICMRA), a forum to support international cooperation among regulators, initiated working groups dedicated to pharmacovigilance and observational studies/real-world evidence on COVID-19 vaccines [58]. This enhanced collaboration has been essential to share knowledge, for instance on case definitions, to align research questions and methods, and to provide consistent information to healthcare professionals and the public.

FUTURE PERSPECTIVES

With SARS-CoV-2 still in circulation, primary or booster vaccinations are still required worldwide. As of June 2022, it was estimated that two thirds of the world population had received at least one dose of a COVID-19 vaccine [59]. It can also be assumed that most people have now been infected with the virus at least once. These high prevalence and vaccination rates increase the complexity of conducting pharmacovigilance and pharmacoepidemiological research about the vaccines, namely delineating the respective roles of COVID-19 infection and vaccination in the onset of some events.

While the safety profile of deployed COVID-19 vaccines appears established, important safety information may still emerge from spontaneous and observational data. Studies are ongoing or planned to further characterise the risk of vaccine-induced myocarditis/pericarditis, including the long-term clinical course [53, 54, 60]. New COVID-19 vaccines based on different platforms, or versions of existing vaccines adapted to specific variants of SARS-CoV-2, will be deployed in the near future. Enhanced levels of safety surveillance remain essential. Insights from ongoing research on TTS/VITT may be relevant for deployed and future vaccines using adenovirus vector platforms [61].

Tools and methods to prioritise and contextualise the reports in EudraVigilance have undergone continual improvement, with automated approaches, routine O/E analyses and monitoring of known signals over time (Figure S1). The extent of masking in EudraVigilance and the need for remediation

methods are being evaluated. New data mining techniques are also being explored, for example the use of machine learning to streamline the adjudication of potential TTS cases.

The pandemic has greatly accelerated the development of safety monitoring tools and methods, regulatory flexibility and efficiency, and scientific collaboration. It is important to maintain the momentum and continue developing, evaluating and customising methods to analyse safety data for the benefit of public health.

HIGHLIGHTS

- Preparedness activities, intensive monitoring and an efficient EU pharmacovigilance network were essential to promptly detect and manage new safety concerns on COVID-19 vaccines, inform healthcare professionals and vaccinees, guide vaccination policy makers and maintain public confidence in the vaccines.
- The extensive use of COVID-19 vaccines has translated into an unprecedented volume of safety data, in particular adverse reaction reports in EudraVigilance. Enhanced signal detection approaches including O/E analyses, have helped triage, prioritise and contextualise the high volume of reports.
- Background incidence rates for AESIs were generated by the EMA-funded ACCESS consortium. EMA also commissioned several observational studies leveraging large multinational networks of healthcare databases to further support the safety monitoring of the vaccines.
- TTS is a new complex syndrome with potentially serious outcome that emerged a few weeks after Vaxzevria was deployed in Europe. There were no specific background incidence rates for TTS but early O/E analyses for CVST, one of the key features of TTS, showed higher than expected ratios, especially in younger vaccinees. A contextualisation exercise revealed that the benefits of Vaxzevria increased with age and infection rates.
- The EU regulatory network was at the forefront of the identification, characterisation and mitigation of the risk of TTS for Vaxzevria and was proactive in dealing with the same risk for Jcovden before the vaccine was deployed in Europe.

  The signal of myocarditis emerged initially from Israel and predominantly affected young male vaccinees after the second dose. These trends were confirmed in EudraVigilance based on case reviews and O/E analyses for both Comirnaty and Spikevax. The risk was later quantified based on large pharmacoepidemiological studies.
- EudraVigilance data and real-world evidence were complementary and instrumental in dealing with new safety concerns, with spontaneous reports allowing to rapidly detect, characterise and communicate about the risks, before further real-world evidence could be generated.

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Table 2 - Main characteristics of the signals of thrombocytopenia with thrombosis syndrome (TTS) and myocarditis/pericarditis

Table 3 - Overview of EMA-funded studies relevant to the risk of thrombosis with thrombocytopenia syndrome

Figure 1 - Generation of real-world evidence from the early COVID-19 pandemic to extended vaccine monitoring
AESI: adverse event of special interest, EU: European Union.

Figure 2 - Observed-to-expected ratios for Vaxzevria and cerebral venous sinus thrombosis (EMA, March 2021)
CVST: cerebral venous sinus thrombosis. O/E: observed-to-expected. CI: confidence interval.
Observed cases extracted from EudraVigilance for the EEA region as of 22 March 2021 (MedDRA preferred terms: Cerebral venous sinus thrombosis, Cerebral thrombosis, Cerebral venous thrombosis, Superior sagittal sinus thrombosis, Transverse sinus thrombosis) and further ascertained manually. Background incidence rates ascertained from the ARS database (Tuscany). Number of vaccinees based on ECDC data as of 21 March 2021. Risk window: 14 days.
O/E ratios over 1 with a lower confidence interval over 1 and below 1 are indicated in red and blue respectively.

Figure 3 - Observed-to-expected ratios for Comirnaty/Spikevax and myocarditis (EMA, June 2021)
O/E: observed-to-expected. CI: confidence interval. Observed cases extracted from EudraVigilance for the EEA region as of 13 June 2021 (MedDRA high level terms 'Infectious myocarditis' and 'Noninfectious myocarditis (incl. myopericarditis)'). Background incidence rates ascertained from the ARS database (Tuscany). Number of vaccinees based on data from ECDC and Member States as of 6 June 2021. Risk window: 14 days.
O/E ratios over 1 with a lower confidence interval over 1 and below 1 are indicated in red and blue respectively.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

Table 1 - Overview of COVID-19 vaccines approved in the European Union as of May 2022

Approval date	Name	MAH	INN / common name	Platform	Target population	Doses administered in the EEA*	Cases in EV from EEA**
21-Dec-2020	Comirnaty	BioNTech Manufacturing GmbH	Tozinameran, COVID-19 mRNA Vaccine (nucleoside modified)	Nucleic acid	5+ years	640 million	786,983
6-Jan-2021	Spikevax	Moderna Biotech Spain, S.L.	Elasomeran, COVID-19 mRNA vaccine (nucleoside-modified)	Nucleic acid	6+ years	152 million	219,135
29-Jan-2021	Vaxzevria	AstraZeneca AB	COVID-19 Vaccine (ChAdOx1-S [recombinant])	Viral vector	18+ years	69 million	276,697
11-Mar-2021	Jcovden	Janssen-Cilag International NV	COVID-19 vaccine (Ad26.COV2-S [recombinant])	Viral vector	18+ years	19.5 million	50,410
20-Dec-2021	Nuvaxovid	Novavax CZ, a.s.	COVID-19 Vaccine (recombinant, adjuvanted)	Protein	18+ years	210,000	964

EEA: European Economic Area; EV: EudraVigilance; INN: International Nonproprietary Name; MAH: Marketing authorisation holder.
* as of 15 May 2022 sourced from the European Centre for Disease Prevention and Control (ECDC); ** as of 29 May 2022

Table 2 - Main characteristics of the signals of thrombocytopenia with thrombosis syndrome (TTS) and myocarditis/pericarditis

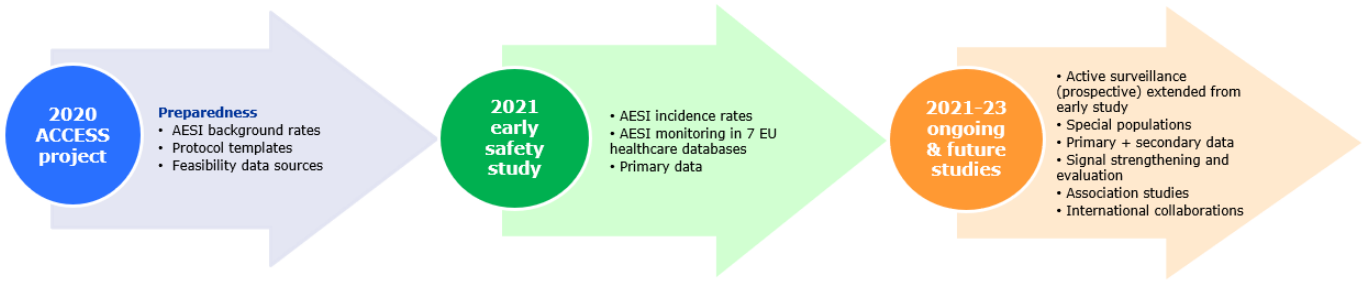
	Thrombosis with thrombocytopenia syndrome	Myocarditis / pericarditis
Origin	Europe	Israel
Vaccines (platform)	Vaxzevria, Jcovden (adenovirus)	Comirnaty, Spikevax (mRNA)
Novelty	New clinical entity	Known conditions
Pre-specified AESI	No	Yes
Background incidence rates	None	ACCESS
Case definition	Several proposed	Brighton collaboration
Risk groups	Not confirmed	Young males
Dose at risk	First dose*	Second dose**
TTO main window (days)	21	14
Public health relevance	Complex new syndrome with high fatality rate that emerged rapidly after start of rollout	Signal in young vaccinees in context of upcoming rollout to paediatric populations
Procedural and regulatory actions	Ad Hoc Expert Group (Vaxzevria) Risk contextualisation (art. 5.3 of reg 726/2004) (Vaxzevria) Update of PI and RMP DHPC	Update of PI and RMP DHPC

ACCESS: vACCine covid-19 monitoring readinESS. AESI: Adverse Event of Special Interest. DHPC: Direct Healthcare Professional Communication. PI: Product Information. RMP: Risk Management Plan. TTO: time-to-onset.
* The risk of TTS after a booster dose of Jcovden or Vaxzevria has not been characterised.
** The risk of myocarditis after a 3rd or booster dose of Spikevax or Comirnaty has not been characterised.

Table 3. Overview of EMA-funded studies relevant to the risk of thrombosis with thrombocytopenia syndrome

Title	Lead	Objectives	Design	Sources / countries	Main findings and limitations
Association between TTS or thromboembolic events, and COVID-19 vaccines [40, 41]	Erasmus and Oxford universities	1) To study the association between COVID-19 vaccine and TTS and VTE; 2) To quantify the association between different COVID-19 vaccine brands and the occurrence of TTS /VTE; 3) To study the association between pre-specified risk factors and the occurrence of VTE/TTS; 4) To characterize treatments used after post-vaccine VTE/TTS; 5) identification of genetic variants associated with venous thromboembolism	Cohort study	Healthcare databases (FR, DE, NL, ES, UK, US)	• 30% increased risk of thrombocytopenia following 1-dose Vaxzevria (vs 1-dose Comirnaty) • double risk of TTS-VTE following Jcovden (vs 1-dose Comirnaty) • 2-to-4-fold increased relative risk of CVST following Jcovden or Vaxzevria • post-vaccine VTE and TTS more common amongst elderly men with specific comorbidities and medicines use • heparin frequently used to manage post-vaccine TTS • genetic determinants of post-vaccination VTE consistent with historical data • confounding by indication is likely to have occurred • anti-PF4 not ascertained • not enough power for CVST
Natural history of coagulopathy and use of anti-thrombotic agents in COVID-19 patients and persons vaccinated against SARS-COV-2 [43, 44, 45]	Erasmus and Oxford universities	To estimate incidence rates of coagulopathy and thromboembolic events in the general population, in COVID-19 patients, and in recipients of COVID-19 vaccines.	Cohort study	Healthcare databases (FR, DE, IT, NL, ES, UK)	• Very low pre-pandemic background rates • Rates of non-vaccine induced TTS appeared higher among older and male individuals and those with more comorbidities and greater medication uptake, compared to the general population.
Impact of EU label changes and regulatory communication on SARS-CoV-2 adenovirus vector vaccines in context of TTS: risk awareness and adherence [46]	Utrecht University	To evaluate the impact of the regulatory actions for Vaxzevria and for Jcovden following the 2021 review, in particular: 1) whether HCPs are aware and know about the risk of TTS when administering these vaccines; 2) whether attitudes of HCPs and general public have changed towards national COVID-19 vaccination programmes; 3) whether national COVID-19 vaccination policies were altered following the regulatory actions.	Web-based questionnaires, semi-structured telephone or online interviews	DK, GR, LV, NL, PT, SI	Study ongoing, results expected in early 2023

CVST: cerebral venous sinus thrombosis, DE: Germany, DK: Denmark, ES: Spain, EU: European Union, FR: France, GR: Greece, IT: Italy, NL: Netherlands, HCP: healthcare professional, LV: Latvia, PT: Portugal, SI: Slovenia, TTS: thrombosis with thrombocytopenia syndrome, VTE: (venous) thromboembolism



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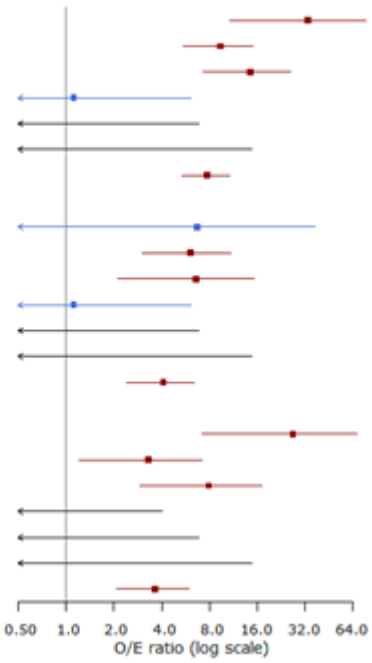
Age group	Expected cases	Observed cases	O/E ratio (95%CI)
CVST			
18-29	0.15	5	33.61 (10.83 - 78.44)
30-49	1.81	17	9.38 (5.46 - 15.02)
50-59	0.76	11	14.55 (7.26 - 26.04)
60-69	0.90	1	1.11 (0.01 - 6.16)
70-79	0.53	0	0.00 (0.00 - 6.89)
80+	0.25	0	0.00 (0.00 - 14.83)
Total	4.40	34	7.73 (5.35 - 10.80)
CVST with thrombocytopenia			
18-29	0.15	1	6.72 (0.09 - 37.40)
30-49	1.81	11	6.07 (3.03 - 10.86)
50-59	0.76	5	6.62 (2.13 - 15.44)
60-69	0.90	1	1.11 (0.01 - 6.16)
70-79	0.53	0	0.00 (0.00 - 6.89)
80+	0.25	0	0.00 (0.00 - 14.83)
Total	4.40	18	4.09 (2.42 - 6.47)
CVST without thrombocytopenia			
18-29	0.15	4	26.89 (7.23 - 68.84)
30-49	1.81	6	3.31 (1.21 - 7.20)
50-59	0.76	6	7.94 (2.90 - 17.28)
60-69	0.90	0	0.00 (0.00 - 4.06)
70-79	0.53	0	0.00 (0.00 - 6.89)
80+	0.25	0	0.00 (0.00 - 14.83)
Total	4.40	16	3.64 (2.08 - 5.91)



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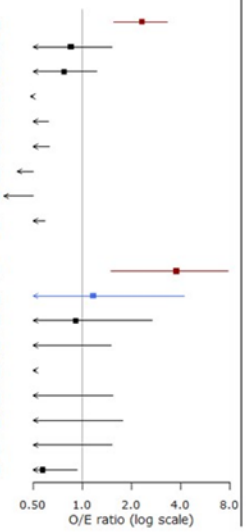
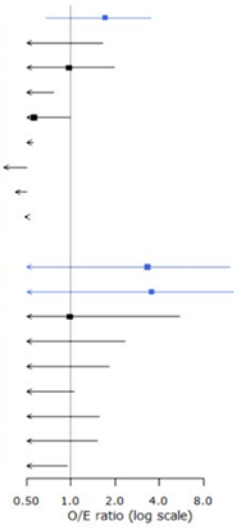
	Males			Females		
Age group	**Expected cases**	**Observed cases**	**O/E ratio (95%CI)**	**Expected cases**	**Observed cases**	**O/E ratio (95%CI)**
Comirnaty						
18-24	13.01	30	2.31 (1.56 - 3.29)	4.10	7	1.71 (0.68 – 3.52)
25-29	12.91	11	0.85 (0.42 – 1.52)	4.39	2	0.46 (0.05 – 1.64)
30-39	23.26	18	0.77 (0.46 – 1.22)	7.25	7	0.97 (0.39 – 1.99)
40-49	32.55	8	0.25 (0.11 – 0.48)	17.11	6	0.35 (0.13 – 0.76)
50-59	45.78	18	0.39 (0.23 – 0.62)	21.47	12	0.56 (0.29 – 0.98)
60-69	27.15	9	0.33 (0.15 – 0.63)	26.17	7	0.27 (0.11 – 0.55)
70-79	29.25	5	0.17 (0.06 – 0.40)	41.74	7	0.17 (0.07 – 0.35)
80+	26.18	3	0.11 (0.02 – 0.33)	24.10	4	0.17 (0.04 – 0.42)
Total	210.1	103	0.49 (0.40 – 0.59)	146.3	55	0.38 (0.28 – 0.49)
Spikevax						
18-24	1.87	7	3.75 (1.50 – 7.73)	0.60	2	3.32 (0.37 – 11.97)
25-29	1.72	2	1.16 (0.13 – 4.20)	0.56	2	3.54 (0.40 – 12.78)
30-39	3.28	3	0.91 (0.18 – 2.67)	1.02	1	0.98 (0.01 – 5.48)
40-49	4.81	2	0.42 (0.05 – 1.50)	2.38	1	0.42 (0.01 – 2.34)
50-59	6.99	0	0.00 (0.00 – 0.52)	3.07	1	0.33 (0.00 – 1.81)
60-69	3.63	1	0.28 (0.00 – 1.53)	3.50	0	0.00 (0.00 – 1.05)
70-79	3.15	1	0.32 (0.00 – 1.77)	4.65	2	0.43 (0.05 – 1.55)
80+	2.43	0	0.00 (0.00 – 1.51)	2.42	0	0.00 (0.00 – 1.51)
Total	27.9	16	0.57 (0.33 – 0.93)	18.2	9	0.49 (0.23 – 0.94)





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