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Original research paper

The readiness of the spontaneous reporting system for COVID-19 vaccines safety monitoring in Croatia

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ABSTRACT

We aimed to identify whether a spontaneous reporting system (SRS) in Croatia could timely identify and confirm signals for COVID-19 vaccines. Post-marketing spontaneous reports of adverse drug reactions (ADRs) following COVID-19 immunisation reported to the Agency for Medicinal Products and Medical Devices of Croatia (HALMED) were extracted and analysed. 6624 cases reporting 30 655 ADRs following COVID-19 immunisation were received from 27th December 2020 to 31st December 2021. Available data in those cases were compared with data available to the EU network at the time when signals were confirmed and minimisation measures were implemented. 5032 cases, reporting 22 524 ADRs, were assessed as non-serious, and 1,592 cases, reporting 8,131 ADRs as serious. The most reported serious ADRs, which were listed in the MedDRA Important medical events terms list, were syncope (n = 58), arrhythmia (n = 48), pulmonary embolism (n = 45), loss of consciousness (n = 43), and deep vein thrombosis (n = 36). The highest reporting rate had Vaxzevria (0.003), followed by Spikevax and Jcovden (0.002), and Comirnaty (0.001). Potential signals were identified, however, they couldn't be timely confirmed solely on cases retrieved by SRS. In order to overcome the limitations of SRS, active surveillance and post-authorisation safety studies of vaccines should be implemented in Croatia.

Keywords: pharmacovigilance, vaccines, COVID-19, adverse drug reactions, spontaneous reporting

Vaccination is one of the most cost-effective health interventions to reduce the incidence of infectious diseases in the human population (1). Thus, the development of COVID-19 vaccines became imperative in the fight against the COVID-19 disease. In Croatia, the vaccination began on 27th December 2020 with vaccine Comirnaty (Marketing

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Authorisation Holder (MAH): BioNTech Manufacturing GmbH), and by the beginning of May 2021 three more COVID-19 vaccines were available: Vaxzevria (MAH: AstraZeneca AB), Spikevax (MAH: Moderna Biotech Spain, S.L) and Jcovden (MAH: Janssen-Cilag International NV).

Clinical trials prior to licensing of COVID-19 vaccines collected key information on efficacy and safety in the general population, however, only limited information on very rare adverse drug reactions (ADRs) was provided (2–5). During the rollout of COVID-19 vaccines, a larger and more diverse population was vaccinated, and more data on the safety of COVID-19 vaccines were obtained, especially on very rare ADRs. They were primarily identified by signal detection performed on data collected by global spontaneous reporting, while characterisation of those ADRs could be further investigated in epidemiological studies, *e.g.*, myocarditis (6–7) and/or additional/follow-up of randomized clinical trials. However, very rare serious ADRs could be both rapidly identified and partially characterised from post-marketing spontaneous reports when specific clinical and laboratory findings were provided, *e.g.*, thrombosis with thrombocytopenia syndrome (TTS) (8).

ADRs are considered signals when available data suggest that there is a new potentially causal association or a new aspect of a known association between ADRs and medicinal products. A spontaneous reporting system (SRS) is one of the common sources of signals (9). Considering very rare serious ADRs or ones with high public interest can influence public confidence in vaccine safety, and consequently result in vaccine hesitancy (10), it is important to have an SRS that is able to identify and provide preliminary data on these ADRs so proper measures could be taken. A previous study analysing safety monitoring of Influenza A/H1N1 pandemic vaccines, which was based on an analysis of data available in the European ADRs database EudraVigilance, concluded that the system based only on spontaneous reporting was not fit-to-purpose and could not timely identify and confirm signals in pandemic settings (11). The authors concluded on the need for a multinational vaccine health outcome resource to assess the epidemiology of potential adverse outcomes, and to quickly evaluate safety signals, estimate the utilization, benefits, and risks of vaccines, and evaluate the effectiveness of public health measures (11). As an outcome of these conclusions, a multi-stakeholder international association Vaccine Monitoring Collaboration for Europe (VAC4EU) was established and used during the COVID-19 pandemic (12). By now, the Croatian safety monitoring system was based only on spontaneous reporting. Therefore, we examined whether SRS established in Croatia could timely identify potential signals and confirm signals for COVID-19 vaccines.

METHODS

In order to establish the readiness of the Croatian safety monitoring system, in timely identification and confirmation of signals for COVID-19 vaccines, post-marketing spontaneous reports of ADRs following immunisation with COVID-19 vaccines and exposure data in Croatia were extracted and analysed. Additionally, available data from Croatia were compared to those on the EU level in terms of maturity to characterise the risk and implement risk minimisation measures (RMMs).

Data source

Data for Croatian cases were obtained from the European database of suspected adverse drug reaction reports – EudraVigilance (EV) (13). EudraVigilance is the system for managing and analysing information on suspected ADRs to medicines, which have been authorised or are being studied in clinical trials in the European Economic Area (EEA). The European Medicines Agency (EMA) operates the EV system on behalf of the European Union (EU) medicines regulatory network. National competent authorities of all EU Member States, including HALMED, have a legal obligation to submit all spontaneously received ADR reports to the EV. The coding of suspected ADRs is performed with the supported versions[1] of the Medical Dictionary for Regulatory Activities (MedDRA) (14) and in line with the applicable recommendations provided in the latest version of the Guide for MedDRA users, MedDRA term selection: Points to consider (15).

Search criteria were set to extract all spontaneously reported cases of suspected ADRs following COVID-19 immunisation, which were received from 27th December 2020 (COVID-19 vaccination start date in Croatia) to 31st December 2021. ADRs were analysed on the preferred term (PT) or other applicable MedDRA level terms (16). Where applicable, Standardised MedDRA Queries (SMQs) were used. SMQs are validated, pre-determined sets of MedDRA terms grouped together after extensive review, testing, analysis, and expert discussion (17).

Vaccine exposure

Data on vaccine exposure were extracted from eVaccination (eVac), which is the central vaccination database of Croatia (owned by the Ministry of Health). Aggregated data, stratified by age, sex, vaccine brand name, dose number, and vaccination date (on week level) for the observed period were provided by the Division for health informatics and Biostatistics of the Croatian Institute of Public Health. Reporting rate was calculated as the number of spontaneously reported cases divided by the number of administered doses in the analysed period.

Data analysis

A descriptive analysis of all retrieved cases was performed. Description of the retrieved cases in terms of patient age and gender, reporter's qualification, case seriousness, categorisation of ADRs according to MedDRA System Organ Class (SOC), and vaccine brand name were done. A test of homogeneity was performed using the chi-squared test to establish whether there is a difference in the distribution of males and females across different COVID-19 vaccines. A one-way ANOVA test was performed to determine whether there is a difference in mean age across different COVID-19 vaccines.

The case was considered serious when at least one of the reported ADRs was serious. According to the definition provided in the Croatian Medicinal Products Act (Official Gazette No. 76/13, 90/14 and 100/18): "Serious adverse reaction/event is any adverse reaction/event that results in death, is life-threatening, requires inpatient hospitalisation or

[1]The latest supported MedDRA versions in the observed period were 23.1, 24.0 and 24.1.

prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or a congenital anomaly/birth defect, is other medically important condition". The seriousness of cases that were initially reported as non-serious was reassessed by HALMED. Seriousness would be changed from non-serious to serious if it was assessed that at least one reported ADR was fulfilling at least one of the previously stated criteria. Criterion other medically important condition was fulfilled if reported ADR was listed in the MedDRA Important medical event terms list[2] (18). The seriousness of cases, which were initially reported as serious by the reporter, was not reassessed by HALMED. Serious ADRs of special interest were assessed on case level, including the level of diagnostic certainty according to Brighton Collaboration (BC) case definition (19, 20), when applicable.

We also compared data that were available in Croatia with data available to the EU network at the time when signals were confirmed and minimisation measures were implemented in the EU according to information available from the EMA website.

Table I. Number of spontaneous cases reported to HALMED and number of COVID-19 vaccine doses administered in the observed perioda in Croatia

COVID-19 Vaccine	No of cases		Exposure (No of doses)
	Serious	Non-serious	
Comirnaty	941	2,785	3,459,575
Vaxzevria	398	1,371	567,347
Spikevax	162	585	445,123
COVID-19 Vaccine Janssen	94	288	188,498
COVID-19 Vaccine	3	5	427
Sex			
M	581	1,453	2,224,087
F	1,005	3,568	2,429,804
UNK	6	11	7,079
Age groups			
0–4	1	5	0
5–11	0	0	421
12–17	8	15	51,542
18–64	1,129	4,298	3,017,040
65–74	180	357	962,504
≥ 75	236	201	629,123
UNK	38	156	340

HALMED – Agency for Medicinal Products and Medical Devices of Croatia; M – male; F – female; UNK – unknown.
[a] Observed period: 27th December 2020 – 31st December 2021

[2] The latest supported MedDRA Important medical event term list versions in the observed period were 23.1, 24.0 and 24.1.

RESULTS AND DISCUSSION

Spontaneously reported ADRs

In the observed period, 6624 cases reporting 30,655 ADRs following COVID-19 immunisation were received. Patients reported 3,656 cases (55.2 %), healthcare professionals 2,938 cases (44.3 %), and in just 30 cases both patient and healthcare professional were reporters. The number of reported serious and non-serious spontaneous cases per vaccine brand name, age, and sex in the context of vaccine exposure for the observed period is presented in Table I. Additionally, distributions of the number of spontaneous cases and number of administered vaccine doses per vaccine brand name throughout the observed period are presented in Fig. 1. The highest reporting rate had Vaxzevria (0.003), followed by Spikevax and Jcovden (0.002), and Comirnaty (0.001). There was a statistically significant difference in the distribution of gender between COVID-19 vaccines (χ^2 (df = 3, N = 6607) = 119.68, $p < 0.01$).

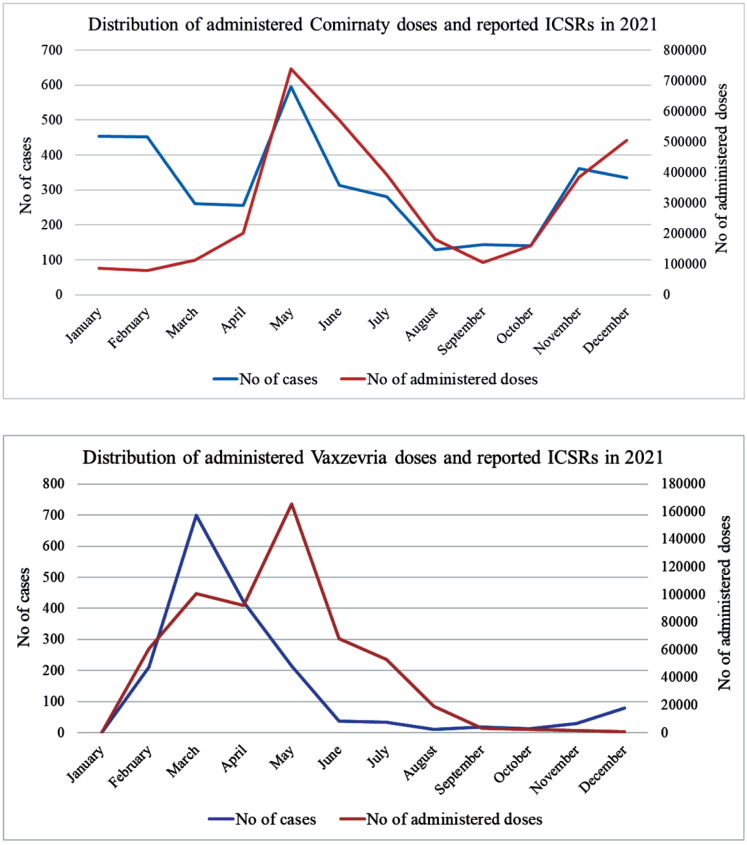

Fig. 1. Distribution of administered COVID-19 vaccine doses, and reported spontaneous cases in Croatia throughout 2021.

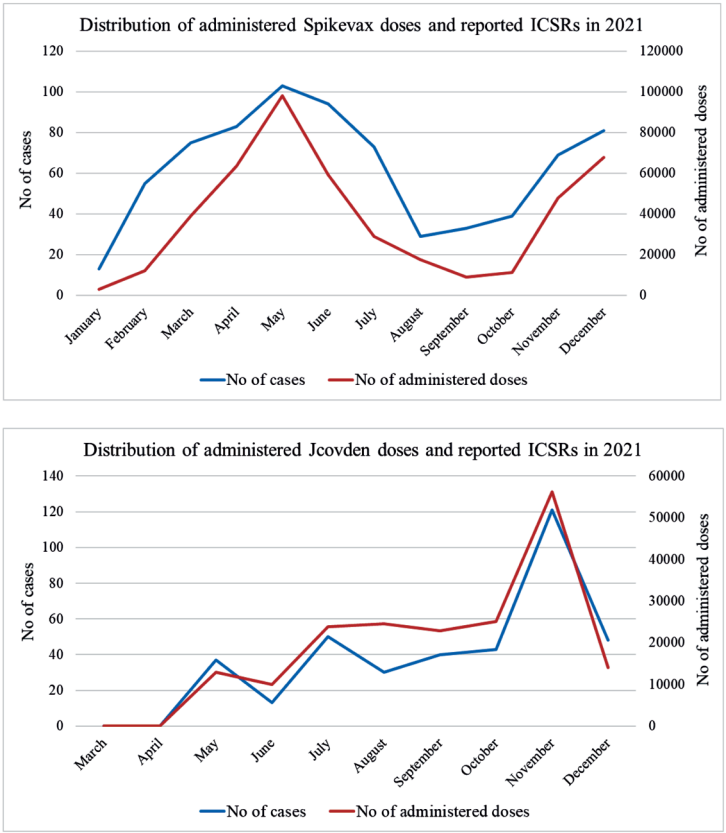

Fig. 1. Continued.

There was a statistically significant difference between mean age across different COVID-19 vaccines as determined by one-way ANOVA ($F(3,6427) = 94.62$, $p < 0.01$).

As many as 5,032 cases (76.0 %), reporting 22,524 ADRs, were assessed as non-serious, and 1,592 cases (24.0 %), reporting 8131 ADRs as serious. In both non-serious and serious cases, the most commonly reported preferred term (PT) was pyrexia, followed by headache, vaccination site pain, chills, myalgia, and fatigue. Out of all reported ADRs, the most reported serious ADRs, which were listed in the MedDRA Important medical events terms list, were syncope ($n = 58$ cases), arrhythmia ($n = 48$), pulmonary embolism ($n = 45$), loss of consciousness ($n = 43$), and deep vein thrombosis ($n = 36$). The distribution of serious and non-serious ADRs per system organ classes (SOCs) is shown in Fig. 2.

Potential signals

Serious cases reporting myocarditis, pericarditis, and Guillain-Barre syndrome (GBS) were reported in the observed period. Data on these cases are presented in Table II.

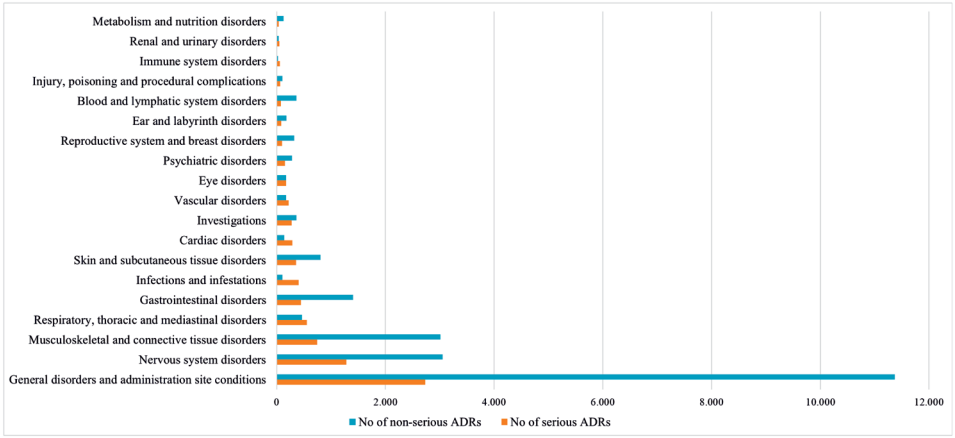

Fig. 2. Distribution of serious and non-serious ADRs per SOCs.

As many as 46 cases reporting arterial embolic and thrombotic events were retrieved, however, in one case it was stated that the event of myocardial infarction was not related to the vaccine administration. All cases were serious and the majority were reported for male patients (n = 30). The mean age was 68 years (SD 16, 95 % CI 11-21). Comirnaty was the most reported suspect COVID-19 vaccine (52.2 %), followed by Vaxzevria (37.0 %) and Spikevax (10.8 %). Healthcare professionals (HCPs) were reporters in the majority of cases (63.0 %). The most commonly reported PTs among cases reporting arterial embolic and thrombotic events were acute myocardial infarction (n = 12 cases), myocardial infarction (n = 8), and transient ischaemic attack (n = 7). The outcome was reported as "recovered" in 4 cases, "recovered with sequelae" in 11 cases, "recovering" in 13 cases, "fatal" in 11 cases, and "unknown" in 7 cases.

Cases reporting venous embolic and thrombotic events (84 cases) were retrieved, out of which 81 cases were serious. The majority were reported as females (n = 44). The mean age was 63 years (SD 14, 95% CI 11-17). Two-thirds of the cases were reported by HCPs. Comirnaty was reported as the suspect COVID-19 vaccine in the majority of cases (52.4 %), followed by Vaxzevria (35.7 %), Spikevax (8.3 %), and Jcovden (3.6 %). The most commonly reported PTs among cases reporting venous embolic and thrombotic events were pulmonary embolism (n = 45 cases) and deep vein thrombosis (n = 36). The outcome was reported as "recovered" in 1 case, "recovered with sequelae" in 3 cases, "recovering" in 56 cases, "not recovered" in 7 cases, "fatal" in 5 cases, and "unknown" in 12 cases.

One case of thrombosis with thrombocytopenia syndrome (TTS) following immunisation with Vaxzevria was identified. The case reported a young adult male patient who had a transient rise in temperature with myalgia and arthralgia on the day of the vaccination, which resolved after 24 h. Nine days after vaccination, the patient was reported to the local hospital for thoracic back pain spreading to the chest. Thrombocytopenia and elevated D-dimers were present at admission. Treatment revealed adrenal vein thrombosis with consequent bleeding and adrenal insufficiency. Furthermore, a clinical picture of one compensated disseminated intravascular coagulation (DIC) was identified. The patient

Table II. Cases reporting myocarditis, pericarditis, and Guillain-Barre syndrome

Adverse drug reaction (no. cases)	Age median (min-max)	Gender (no. cases)	Time to onset median (min-max)	Number of doses (no. cases)	Vaccine brand name (no. cases)	Reporter (no. cases)	Brighton criteria – diagnostic criteria (no. cases)	Outcome (no. cases)
Myocarditis *n* = 7	26 years (19–55 years)	Male, *n* = 6 Female, *n* = 1	22 days (2–42 days)	1st dose, *n* = 1 2nd dose, *n* = 5 Unknown, *n* = 1	Comirnaty *n* = 6 Spikevax *n* = 1	HCP, *n* = 4 Patient, *n* = 1 HCP/patient *n* = 1 MAH, *n* = 1	Level 2 (probable) *n* = 2 Level 4 (insufficient evidence), *n* = 4	Recovering/ resolving *n* = 5 Recovered/resolved with sequelae, *n* = 1 Unknown, *n* = 1 case
Pericarditis *n* = 11	44 years (19–74 years)	Male, *n* = 4 Female *n* = 7	11 days (2–97 days)	1st dose, *n* = 6 2nd dose, *n* = 4 Unknown, *n* = 1	Comirnaty *n* = 9 Spikevax *n* = 1 Vaxzevria *n* = 1	HCP, *n* = 6 Patient, *n* = 5	Level 2 (probable) *n* = 3 Level 3 (possible) *n* = 2 Level 4 (insufficient evidence) *n* = 6	Recovered/resolved *n* = 1 Recovering/ resolving *n* = 5 Not recovered/not resolved, *n* = 2 Unknown, *n* = 3
Guillain-Barre syndrome (GBS), *n* = 6	49 years (24–70 years)	Male, *n* = 2 Female *n* = 4	16 days (1–22 days)	1st dose, *n* = 5 2nd dose, *n* = 1	Comirnaty *n* = 3 Vaxzevria *n* = 2 Jcovden *n* = 1	HCP, *n* = 3 Patient, *n* = 2 HCP/patient *n* = 1	Level 1 (certain) *n* = 3 Level 2 (probable) *n* = 1[a] Level 3 (possible) *n* = 1 Not fulfilling criteria *n* = 1	Recovering/ resolving *n* = 5 Not recovered/not resolved, *n* = 1

HCP – health care professional; MAH – marketing authorisation holder.

[a] One case of Miller-Fisher syndrome fulfilled all criteria for a level 2 case except bilateral reduced or absent tendon reflexes and ataxia, which were not diagnosed.

developed a headache and sagittal sinus thrombosis with consequent intracerebral haemorrhage, resulting in death. The patient had no previous severe infections, except for increased nasal secretion. There were no clinical or laboratory signs of sepsis. Considering the typical time window between vaccination and onset symptoms, decrease in platelet counts, positive anti-PF4/heparin ELISA test (performed *post-mortem*), severe, delayed onset headache, and adrenal haemorrhage following thrombosis in the small adrenal veins, it was concluded that clinical picture was highly suggestive for TTS and that it was likely that it had been induced by vaccination with Vaxzevria.

Two potential cases of acute disseminated encephalomyelitis (ADEM) were identified. Both cases were reported after the first dose of the COVID-19 vaccine, one after Comirnaty and one after Vaxzevria. According to the Brighton criteria, a fatal case reported for an elderly male patient was a level 2 case, however, it was not possible to exclude clear alternative acute infections or other diagnoses for illness. Another case reported for a young adult female patient, who recovered, did not fulfil Brighton criteria for ADEM.

In the observed period, 204 cases (3.0 %) of females reported ADRs pertaining highest level group term (HLGT) menstrual cycle and uterine bleeding disorders. The mean age was 36 years (SD 8, 95% CI 7-9). The majority of cases were non-serious (77.9 %) and reported by patients (68.6 %). The most reported suspect COVID-19 vaccine was Comirnaty (76.0 %), followed by Spikevax (10.8 %), Vaxzevria (7.4 %), and Jcovden (5.8 %). Most commonly reported PTs pertaining HLGT menstrual cycle and uterine bleeding disorders were menstrual disorder ($n = 66$ cases), heavy menstrual bleeding ($n = 59$), polymenorrhea ($n = 45$), amenorrhoea ($n = 32$), dysmenorrhoea ($n = 30$), oligomenorrhea ($n = 28$), irregular menstruation ($n = 26$), intermenstrual bleeding ($n = 21$) and delayed menstruation ($n = 16$). The outcome was reported as "recovered" in 53 cases, "recovered with sequelae" in 2 cases, "recovering" in 42 cases, "not recovered" in 38 cases, and "unknown" in 69 cases.

A comparison of data that were available in Croatia with data available to the EU network at the time of signals confirmation is presented in Table III.

Special populations

Analysis of cases reported for paediatric population identified 29 cases, out of which 9 were serious. Six (6) cases, out of which 5 were reported by patients, were reported for children aged between 1 and 14 months. These cases were parent-child reports, with PT exposure *via* breast milk coded. The suspect COVID-19 vaccine was Comirnaty in 5 cases, while the brand name was not known in 1 case. Most reported PT was pyrexia. One case reporting pyrexia, rhinorrhoea, and cough was reported as serious by the patient, whereas other cases were non-serious. The outcome was "recovered" in 4 cases, including a serious case, and "unknown" in 2 cases. Twenty-three (23) cases were reported for adolescents (12–17 years). Comirnaty was the suspect COVID-19 vaccine in 19 cases, Spikevax in 3 cases, and Jcovden in 1 case; 11 cases were reported for female patients and 12 for male patients. The most reported PT was pyrexia, followed by headache, vaccination site pain, and fatigue. Out of 8 serious cases, 4 were reported by patients, 3 by physicians, and 1 by other HCP. Two (2) out of 8 cases reported vaccination failure and COVID-19 disease. In 4 serious cases following important medical event terms were reported: syncope ($n = 1$), hemiparesis ($n = 1$), hallucination and epilepsy ($n = 1$), and myoclonic epilepsy and status epilepticus ($n = 1$). In the remaining 2 serious cases, no important medical event was reported, however, the

Table III. Comparison of data available in Croatia with data available to the EU network at the time of signals confirmation in the observed period[a]

Signals	COVID-19 Vaccine	Date of signal confirmation in the EU	Available data in Croatia at the time of signal confirmation	Available data in the EU based on which signal was confirmed
Thrombosis with thrombocytopenia syndrome (TTS)	Vaxzevria (MAH: AstraZeneca AB)	07 April 2021	1 case received in March 2021 with limited data so the diagnosis of TTS could not be initially confirmed; follow-up was requested and additional data were received after the signal was confirmed on the EU level upon which TTS was confirmed	Analysis of spontaneous cases supported with observed to expected (O/E) analysis.[b] The expected number of events (background incidence) was calculated using large EU healthcare databases. Specific clinical and laboratory findings were provided, but not for all cases. A total of approx. 15 cases of thromboembolic events combined with thrombocytopenia associated with the use of Vaxzevria were initially identified. Further epidemiological studies for better characterisation of this risk were proposed, including studies on large healthcare databases and a prospective cohort study "Safety monitoring of COVID-19 vaccines in the EU" (ROC20).
Myocarditis/ pericarditis	Comirnaty (MAH: BioNTech Manufacturing GmbH) Spikevax (MAH: MODERNA BIOTECH SPAIN, S.L)	8 July 2021	1 spontaneous case of myocarditis with limited information was identified by 8th July 2021 4 spontaneous cases of pericarditis were received by 8th July 2021, however, these cases alone were not sufficient for signal confirmation	Analysis retrieved that 358 cases reported myocarditis and 296 cases of pericarditis. Analysis of those cases was supported by observed to expected (O/E) analysis.[c] The expected number of events (background incidence) for myocarditis was calculated using large EU healthcare databases. A constant background rate of pericarditis was used. Diagnosis of myocarditis/pericarditis was confirmed using Brighton's collaboration (BC) criteria. Post-authorisation safety studies were requested for further characterisation of these risks.
Guillain-Barré syndrome (GBS)	Vaxzevria (MAH: AstraZeneca AB)	2 September 2021	1 spontaneous case was reported on 2nd September 2021	833 cases were reported under SMQ narrow Guillain-Barré syndrome.[d] Analysis of those cases was supported by observed to expected (O/E) analysis. The expected number of events (background incidence) for GBS was calculated using large EU healthcare databases. The diagnosis was confirmed using Brighton's collaboration (BC) criteria. Post-marketing observational study using existing secondary health data sources and non-interventional studies were implemented for further characterisation of the risk.

Signals	COVID-19 Vaccine	Date of signal confirmation in the EU	Available data in Croatia at the time of signal confirmation	Available data in the EU based on which signal was confirmed
Venous thromboembolism (VTE)	Jcovden (MAH: Janssen-Cilag International NV	30 September 2021	No spontaneous cases reporting venous thromboembolism were identified by 30th September 2021	The signal was confirmed based on the available data from clinical trials supported with data from the post-marketing setting, both of spontaneously reported cases as well as observational data.[e] Further characterisation of the risk was imposed through ongoing clinical trials and post-authorisation safety studies.
Cerebrovascular venous and sinus thrombosis (CVST) without thrombocytopenia	Vaxzevria (MAH: AstraZeneca AB)	3 November 2021	1 spontaneous case received in April 2021	Cumulatively, 458 cases of CVST without thrombocytopenia have been reported.[f] Analysis of those cases was supported by observed to expected (O/E) analysis. The expected number of events (background incidence) for CVST was calculated using large EU healthcare databases.

EU – European Union; MAH – Marketing Authorisation Holder

[a] Observed period: 27th December 2020 – 31st December 2021

[b] European Medicines Agency (EMA), *Signal assessment report on embolic and thrombotic events (SMQ) with COVID-19 Vaccine (ChAdOx1-S [recombinant]) – COVID-19 Vaccine AstraZeneca (Other viral vaccines)*, April 2021; https://www.ema.europa.eu/en/documents/prac-recommendation/signal-assessment-report-embolic-thrombotic-events-smq-covid-19-vaccine-chadox1-s-recombinant_en.pdf; last access January 25, 2023

[c] European Medicines Agency (EMA), *Updated Signal assessment report on Myocarditis, pericarditis with Tozinameran (COVID-19 mRNA vaccine (nucleoside-modified) – COMIRNATY)*, September 2021; https://www.ema.europa.eu/en/documents/prac-recommendation/updated-signal-assessment-report-myocarditis-pericarditis-tozinameran-covid-19-mrna-vaccine_en.pdf; last access January 25, 2023

[d] European Medicines Agency (EMA), *COVID-19 vaccine safety update: VAXZEVRIA*, September 2021; https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/covid-19-vaccine-safety-update-vaxzevria-previously-covid-19-vaccine-astrazeneca-8-september-2021_en.pdf; last access January 25, 2023

[e] European Medicines Agency (EMA), *COVID-19 vaccine safety update: COVID-19 VACCINE JANSSEN*, October 2021; https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/covid-19-vaccine-safety-update-covid-19-vaccine-janssen-6-october-2021_en.pdf; last access date January 25, 2023

[f] European Medicines Agency (EMA), *COVID-19 vaccine safety update: VAXZEVRIA*, November 2021; https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/covid-19-vaccine-safety-update-vaxzevria-previously-covid-19-vaccine-astrazeneca-11-november-2021_en.pdf; last access date January 25, 2023

reporter marked one of the seriousness criteria. The outcome was reported as "recovered" in 10 cases, "recovered with sequelae" in 1 case, "recovering" in 7 cases, "not recovered" in 1 case, and "unknown" in 4 cases.

For pregnant women 13 cases were reported, out of which 5 were serious; 12 cases were reported by patients and one by a pharmacist. Comirnaty was reported as the suspect COVID-19 vaccine in 11 cases, while in the remaining 2 cases Vaxzevria and Jcovden were reported, resp. Most reported PT was vaccination site pain ($n = 7$), followed by fatigue ($n = 4$) and headache ($n = 3$). Important medical events reported in serious cases were PT spontaneous abortion ($n = 4$) and suicidal behaviour ($n = 1$). The outcome was "recovered and/or recovering" in 9 cases, "recovered with sequelae " in 1 case, not recovered in 1, and "unknown" in 2 cases.

DISCUSSION

Information gathered by SRS showed that the majority of reported post-marketing ADRs were non-serious. Most reported ADRs in both serious and non-serious cases were pyrexia, headache, vaccination site pain, chills, myalgia, and fatigue, which is in line with data reported from clinical trials (21–23). Only limited information on COVID-19 vaccines' safety in the paediatric population and pregnant women was identified. Although spontaneously reported ADRs were generally in line with the known safety profile of COVID-19 vaccines (24–29), potential signals were identified in both special populations.

Two cases reported suspected epileptic seizures in adolescent patients, however, one patient already had a history of similar seizures, and in another case, limited information was provided. Since incidence rates of epilepsy in childhood range from approximately 0.5 to 8 per 1,000 person-years, and it is estimated that 0.5 to 1 percent of children and adolescents will experience at least one afebrile seizure by adolescence age (30–33), it cannot be excluded that epileptic seizures in both cases had alternative aetiology. Considering no additional data, which would indicate a causal relationship between epileptic seizures and COVID-19 vaccines, were identified at the time, the signal was not confirmed. Analysis of spontaneously reported cases in pregnant women identified four cases of spontaneous abortion. In all 4 cases, spontaneous abortion occurred in the first trimester (between the 4^{th} and 8^{th} week of pregnancy). Although it is not possible to assess a causal relationship in those cases, it should be pointed out that spontaneous abortion is the most common complication in early pregnancy (34). The incidence of first-trimester pregnancy loss is as high as 31 %, though that incidence decreases to approximately 10 % when considering only losses occurring in clinically recognized pregnancies (35, 36). In addition, currently available data on the safety profile of COVID-19 vaccines in pregnancy found no evidence of an increased risk for early pregnancy loss after COVID-19 vaccination (37–39). Thus, this signal was not confirmed. One case reported suicidal behaviour following COVID-19 vaccination in a pregnant woman (second trimester), however, the patient had previously been diagnosed with a psychiatric disorder. A review of scientific literature and analysis of available data in the EudraVigilance did not identify additional information that would confirm this signal.

In the general population, several ADRs of special interest (*e.g.*, Guillain-Barre syndrome (GBS) and ADEM) and potential signals (*e.g.*, menstrual disorders, myocarditis/

pericarditis, thromboembolic events, TTS) were also identified. Although never before such a large number of spontaneously reported cases had been received for vaccines, or even for all medicinal products together, in a 1-year period,[3] data on very rare ADRs were scarce (Table III). In addition, the majority of identified cases reporting very rare ADRs lacked information on specific clinical and laboratory findings. Thus, assessment of the causal relationship, and consequently confirmation of signals and implementing risk minimisation measures, was not possible at the time, based solely on Croatian reports. However, those cases were sent to the EU ADRs database (EudraVigilance) and together with spontaneously reported cases from other Member States provided sufficient data for the timely identification of signals on the EU level. After a thorough assessment of all available data, those signals were confirmed or not confirmed concurrently in all Member States, including Croatia. In addition, based on data available in those cases, new RMMs for COVID-19 vaccines were proposed.

It should be highlighted that one of the limitations of this study was that the analysed spontaneous reporting data could not be used to compare the safety profiles of different COVID-19 vaccines. These data only provided information on the ADR reporting rate (number of spontaneously reported cases divided by the number of administered doses). Reporting rate cannot be interpreted as an ADR incidence rate since it is subject to various biases including under-reporting and over-reporting (40). The majority of spontaneously reported cases (56.0 %) in the Croatian ADRs database were reported following immunisation with Comirnaty. This was expected since Comirnaty was the most frequently administered COVID-19 vaccine in Croatia (74 % of all administered COVID-19 vaccine doses). However, Vaxzevria had the highest reporting rate (0.003), whereas Comirnaty had the lowest (0.001). This could potentially be a result of negative publicity that surrounded Vaxzevria in early March 2021, when mass media throughout Europe reported that five people had died following immunisation. It was observed that the highest numbers of spontaneous cases after Vaxzevria were reported in March (699 cases) and April (421 cases) 2021, although most doses (165,597) were administered in May 2021 (214 cases) (Fig. 1). Furthermore, homogeneity tests showed that there was a statistically significant difference in gender distribution and mean age between different COVID-19 vaccines. These results indicated that populations reporting ADRs for different COVID-19 vaccines were not the same so a comparison of safety profiles of COVID-19 vaccines solely based on these data would not be appropriate. In addition, these data do not include data from patients who did not experience any ADR so comparison of safety profiles would be confounded by selection bias.

Real-world data, based on the use of electronic medical records and health claims, has proven useful to better identify and further characterise very rare ADRs like TTS (41). Similarly, a causal relationship between signals could be confirmed (*e.g.* thromboembolism with adenovirus COVID-19 vaccines (Vaxzevria and Jcovden)) and/or further characterisation of those signals performed (*e.g.* myocarditis/pericarditis with COVID-19 mRNA vaccines (Comirnaty and Spikevax)) only after data from observational studies and randomized clinical trials became available worldwide (6–7, 42–52). Thus, active surveillance and post-authorisation safety studies should be implemented in order to overcome the limitations

[3]https://www.halmed.hr/Farmakovigilancija/Izvjesca-o-nuspojavama/

of SRS and consequently improve the safety surveillance system in Croatia. A non-interventional post-authorisation study of prospective monitoring of COVID-19 vaccines' safety was conducted in Croatia. The results of this study will be assessed to establish whether collected data could overcome the limitations of SRS.

CONCLUSIONS

Information gathered by SRS confirmed known safety profiles of COVID-19 vaccines and enabled the detection of potential signals. Nevertheless, these signals couldn't be confirmed solely on Croatian spontaneous case reports. In addition, a potential influence of media and news on spontaneous reporting was observed. In order to overcome the limitations of SRS, active surveillance and post-authorisation safety studies that can estimate rates and facilitate risk evaluation should be implemented in the safety surveillance system in Croatia.

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