Therapie xxx (xxxx) xxx—xxx

Disponible en ligne sur ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com

PHARMACOVIGILANCE

The enhanced national pharmacovigilance system implemented for COVID-19 vaccines in France: A 2-year experience report

Samuel Crommelynck[a,*], Aurélie Grandvuillemin[b,1], Claire Ferard[c], Céline Mounier[c], Nathalie Gault[d], Evelyne Pierron[c], Baptiste Jacquot[c], Tiphaine Vaillant[d], Isabelle Parent du Chatelet[a,e], Alexis Jacquet[a], Francesco Salvo[f,g,1], Martine Alt[h,1], Haleh Bagheri[i,1], Joëlle Micallef[j,1], Antoine Pariente[f,1], Sophie Gautier[k,1], Marie-Blanche Valnet-Rabier[l,1], Marina Atzenhoffer[m,1], Marion Lepelley[a,n], Judith Cottin[a,m,1], Isabelle Lacroix[a,i], Valérie Gras[a,o], Nathalie Massy[p,1], Alban Dhanani[a], Philippe Vella[a], Youssef Shaim[a], Laurence Baril[a,e], Annie-Pierre Jonville-Béra[a,q], Mehdi Benkebil[c], the 30 French Regional Pharmacovigilance Centres[1]

[a] *French National Agency for Medicines and Health Products (ANSM), Direction for Medical Drugs Department, Department of Infections and Emerging Disease, 93200 Saint-Denis, France*
[b] *Regional Pharmacovigilance Centre of Burgundy, University Hospital Dijon Bourgogne, 21000 Dijon, France*
[c] *French National Agency for Medicines and Health Products Safety, ANSM, Direction for Surveillance, 93200 Saint-Denis, France*
[d] *French National Agency for Medicines and Health Products Safety, ANSM, General Direction for Operations, PRAC representative, 93200 Saint-Denis, France*
[e] *Santé Publique France, Infectious Diseases, 94410 Saint-Maurice, France*
[f] *Regional Pharmacovigilance Centre of Bordeaux, DROM, University Hospital of Bordeaux, 33000 Bordeaux, France*
[g] *UMR 1219 Pharmacoepidemiology Team, Bordeaux Population Health Research Centre, Inserm, University of Bordeaux, 33000 Bordeaux, France*

* Corresponding author. French National Agency for Medicines and Health Products (ANSM), Direction for Medical Drugs Department, Department of Infections and Emerging Disease, 143, boulevard Anatole-France, 93200 Saint-Denis, France
Adresse e-mail : samuel.crommelynck@ansm.sante.fr (S. Crommelynck).
[1] French Regional Pharmacovigilance Centres Network (RPVC) https://www.rfcrpv.fr.

https://doi.org/10.1016/j.therap.2024.11.002

Pour citer cet article : S. Crommelynck, A. Grandvuillemin, C. Ferard et al., The enhanced national pharmacovigilance system implemented for COVID-19 vaccines in France: A 2-year experience report, Therapies, https://doi.org/10.1016/j.therap.2024.11.002

[h] *Regional Pharmacovigilance Centre, University Hospital of Strasbourg, 67091 Strasbourg, France*
[i] *Department of Medical and ClinicalPharmacology, Centre of Pharmacovigilance, Pharmacoepidemiology and Informations on Medications, Inserm UMR 1027, University Hospital and Faculty of Medicine, 31000 Toulouse, France*
[j] *Department of Clinical Pharmacology and Pharmacovigilance, Regional Pharmacovigilance Centre of Marseille, AP—HM, 13000 Marseille, France*
[k] *Departement of Clinical Pharmacology, University Hospital, Regional Pharmacovigilance Centre of Lille, 59000 Lille, France*
[l] *Regional Pharmacovigilance Centre of Franche-Comté, University Hospital of Besançon, 25000 Besançon, France*
[m] *University Hospital Department of Pharmacotoxicology, Regional Pharmacovigilance Centre, Civil Hospices of Lyon (HCL), 69003 Lyon, France*
[n] *Regional Pharmacovigilance Centre, University Hospital of Grenoble-Alpes, 38000 Grenoble, France*
[o] *Pharmacovigilance Centre, Department of Clinical Pharmacology, Amiens Picardie University Medical Centre, 80054 Amiens, France*
[p] *Regional Pharmacovigilance Centre, Clinical Pharmacology Department, Rouen University Hospital, 76031 Rouen, France*
[q] *Departement of Pharmacosurveillance, University Hospital, Regional Pharmacovigilance Centre Val-de-Loire, 37000 Tours, France*

Reçu le 24 septembre 2024 ; accepté le 4 novembre 2024

KEYWORDS
COVID-19 vaccines ;
Pharmacovigilance ;
Enhanced surveillance ;
Adverse drug reaction ;
Safety signal ;
Benefit-risk assessment

Summary In March 2020, World Health Organization recognized severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emergence as a public health emergency of international concern. One of the major preventative measures developed against coronavirus disease 2019 (COVID-19) was vaccines. To monitor their use and safety of vaccines from the first utilization in humans during clinical development phases to implementation for the general population, an enhanced national pharmacovigilance system was enabled by the French National Agency for Medicines and Health Products Safety in collaboration with the 30 Regional Pharmacovigilance Centres. Here, we review the significant outcomes from a 2-year collaboration experience between the French National Agency for Medicines and Health Products Safety, the 30 Regional Pharmacovigilance Centres, disease-related experts and the pharmacovigilance and risk assessment committee at the European medicine agency. In France, until January 2023, over 155 million doses of COVID-19 vaccines were administrated, and 190,000 adverse events following immunizations (25% classified as serious) were analysed. Altogether 53 potential safety signals were reported to the Pharmacovigilance and Risk Assessment Committee at the European Medicine Agency by the French National Agency for Medicines and Health Products Safety: 13 were confirmed, 24 are still under investigation and 16 were not confirmed. The enhanced national PV system contributed actively better to define the safety profile of the newly developed vaccines, and the French National Agency for Medicines and Health Products Safety continues to monitor the benefit and risks of the COVID-19 vaccines.

Abbreviations

ANSM	French National Agency for Medicines and Health Products Safety
CHMP	Committee for Medicinal Products for Human Use
CNAM	*Caisse nationale d'Assurance maladie*
EC	European Commission
COVID-19	coronavirus disease 2019
EMA	European Medicines Agency
HAS	Haute autorité de santé
MERS-CoV	Middle East respiratory syndrome coronavirus
mRNA	messenger RNA
PRAC	Pharmacovigilance Risk Assessment Committee
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

What was the organisation set up at European level to assess continuous benefit and risk of the newly developed vaccines against COVID-19?

Recognized between March 2020 and early May 2023 as a public health emergency of international health concern by the World Health Organization, the mobilization and the response to the coronavirus disease 2019 (COVID-19) pandemic was unique in the modern global health era. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 virus) was a newly identified emerging pathogen with respiratory transmission ability in symptomatic but also asymptomatic individuals. This transmission pattern was different from the other recent coronavirus emergences (SARS-CoV-1 and Middle East respiratory syndrome coronavirus — MERS-CoV) in humans and partly explained the magnitude of the pandemic. The first recognized viral variants have led to a high disease burden and deaths in the more fragile adults and elderly population, together with an overloading of the health care systems in many countries. One of the major preventative measures against COVID-19 severe disease and death cases was the use of vaccines, but the vaccines have had to be developed in an extraordinarily short period by the pharmaceutical industry.

Vaccine manufacturers developed four technological platforms: the messenger RNA (mRNA), adenovirus — and protein-based, and inactivated vaccines. The European Union (EU) decided to coordinate access to COVID-19 vaccines by accelerating the marketing authorizations together with joint vaccine procurement mechanisms. The European Medicines Agency (EMA) had a key role in the implementation of accelerated procedures (so-called ''rolling review'' process) [1] to ensure conditional approvals for early access to vaccines. All the national medicines agencies, including the French National Agency for Medicines and Health Products Safety (ANSM), contributed greatly to the rolling review process of the candidate vaccines by sharing the review of the submitted files in a prompt manner. This continued review of the quality, safety and efficacy data was a key component of the benefit-risk assessment for each candidate vaccine. In addition, some medicines agencies, including ANSM, accelerated the vaccine lots' release as official medicines control laboratories.

Implementation of the vaccines against COVID-19 and implication on the pharmacovigilance system in France

Between December 2020 and March 2021, 2 mRNA vaccines (Comirnaty®, tozinameran from Pfizer and Spikevax®, elasomeran from Moderna) and 2 adenovirus-based vaccines (Vaxzevria®, ChAdOx1-S [recombinant] from Oxford-AstraZeneca and JCovden®, Ad26.COV2-5 [recombinant] from Janssen) were authorized by the European Commission (EC) after positive opinions from the Committee for Medicinal Products for Human Use (CHMP) at the EMA.

In December 2021, the first adjuvanted recombinant-protein-based vaccine (Nuvaxovid®, COVID-19 [recombinant, adjuvanted] from Novavax) was made available to the population. Then, in June 2022, the first adjuvanted inactived vaccine (VLA2001 from Valneva) was authorized for use. It was also the first vaccine where immunogenicity data were used (the comparator was Vaxzevria®) by the market authorisation holder for registration. For the mRNA vaccines, adapted vaccines to new variants (namely Omicron variant) were also registered for use during the summer 2022 and 2023. A second adjuvanted recombinant-protein-based vaccine based on the Beta variant (Vidprevtyn® Beta from Sanofi Pasteur) was authorized in November 2022 as a booster dose. A third one based on the Beta and Alpha variants (Bimervax® from Hipra) was approved in March 2023 for use as a booster.

Despite the operational and logistical challenges due to the magnitude of the target population, the implementation of the COVID-19 vaccines was successfully addressed by the European countries. In parallel with the vaccine implementation campaign, in France, the pharmacovigilance was also a challenge to address with the need to build an enhanced national pharmacovigilance surveillance system in collaboration with the 30 Regional Pharmacovigilance Centres Network [2]. In addition, to report and inform on adverse event following immunization and potential safety signal assessment in near-real time, ANSM was working closely with the French national immunization technical advisory groups also known as ''*Comité technique des vaccinations*'' coordinated by the *Hauteautorité de santé* (HAS) to adapt their recommendations according to the most updated safety evidences.

What are the key elements of the vaccine pharmacovigilance in Europe and in France?

All vaccine development plans include well-defined post-authorization activities described in the risk management plan agreed between the market authorisation holder and the regulatory authorities. The coordination is done under the auspices of the CHMP and the Pharmacovigilance Risk Assessment Committee (PRAC) by EMA. Those risk management plans are amended as necessary with the acquisition of new safety and efficacy data and with the use of the vaccines in new age groups. Those pharmacovigilance activities are based on periodic safety reports (initially on a monthly timing, then bi-monthly and today bi-annual for each of the COVID-19 vaccines) and included post-authorisation safety studies and post-authorisation efficacy/effectiveness studies.

For COVID-19 vaccines, the scale of the targeted populations to be vaccinated against this emerging viral pathogen led to the set-up of a unique enhanced national pharmacovigilance system under the coordination of the ANSM [3—6]. Covering all French regions including overseas territories, the 30 Regional Pharmacovigilance Centres Network played an essential role in analysing the reported adverse drug events, identifying potential adverse event following immunizations and assessing potential safety signal assessment, and monitoring recognized adverse event following immunizations. Adverse event following immunizations

were mostly reported by the health care professionals or by the vaccinated individuals contacting directly the Regional Pharmacovigilance Centres (legally possible in France since 2001). During the national vaccination campaign against COVID-19, these notifications mainly were digital and supported by different means of lay and professional communications to encourage adverse event following immunization notifications.

Those notifications were documented and analysed by the 30 Regional Pharmacovigilance Centres Network experts and when validated, the data were recorded in the national pharmacovigilance database [7] managed by ANSM. As they routinely do for all marketed drugs in the context of the Regional Pharmacovigilance Centres Network core missions, Regional Pharmacovigilance Centres experts also provided direct support to the health care professionals and/or individuals for adverse event care management, for handling vaccination in patients who experienced adverse event following immunizations after receiving prior injections, or for patients with specific conditions (e.g. pregnant women) [3]. In addition, leading Regional Pharmacovigilance Centres of each vaccine were responsible for the daily analysis of all cases recorded in the national pharmacovigilance database for carrying out periodic quantitative descriptive analyses of the corresponding reports, and periodic qualitative expert summaries of the reports of interest completed by a scientific targeted bibliographical search. Pharmacovigilance experts have monitored and analysed the adverse event following immunizations of COVID-19 vaccines in the special populations of pregnant and breastfeeding women. A collegial assessment including ANSM, Regional Pharmacovigilance Centres and disease-related experts supported the classification of outstanding reports into potential or confirmed safety signals. ANSM also transferred all adverse event following immunizations from the French national pharmacovigilance database to the Eudravigilance system [8] managed by EMA. All these adverse event following immunizations are categorized by effects coded with MedDRA dictionary, seriousness, time to onset and age and gender of the person who was experiencing this adverse event following immunization. The number and seriousness of adverse event following immunizations reported in France with each COVID-19 vaccine from December 21, 2020 to December 31, 2022 are presented Figs. 1—3.

The ANSM also shared information with the other EU member states, usually through the recurrent safety reports or through an alert mechanism with the dedicated procedure of European pharmacovigilance issues tracking tool [9]. The content of the shared information can be some ''remarkable reports'' of particular concern, conclusion of a national pharmacovigilance survey or a pharmaco-epidemiological study report. The PRAC reviewed all existing safety information (including scientific literature) and might have recommended updating the product information (summary of product characteristics and package leaflet), implementing other risk minimization measures, and/or informing the citizens, health care professionals and public health decision-makers as appropriate.

Within the enhanced pharmacovigilance system that was set-up in French, 13 Regional Pharmacovigilance Centres were particularly mobilized for the safety monitoring of the COVID-19 vaccines. Two Regional Pharmacovigilance Centres were designated initially to analyse the incoming adverse event following immunizations at national level for each vaccine (finally extended to four Regional Pharmacovigilance Centres for Comirnaty® due to the wide predominance of its use in France). Additionally, two Regional Pharmacovigilance Centres were missioned to monitor adverse event following immunization occurring in pregnant and breastfeeding women for all vaccines, two were missioned to monitor more closely adverse event following immunization occurring with heterologous vaccine scheme, and two were missioned to coordinate actions, efforts and communications between all ''monitoring Regional Pharmacovigilance Centres teams''. They all shared their investigational reports to all Regional Pharmacovigilance Centres and ANSM weekly for the first 8 months of the vaccine campaign, twice a month during the following 8 months, then on a monthly basis for an additional 8 months, and currently twice a year for mRNA vaccines. After each collegial meeting, a communication was prepared to the health care professionals together with a lay summary for the citizens and was posted on the ANSM website (an example of such communication is given in [10]).

What were the main outcomes after 2-year of implementation of the French enhanced national PV system?

From December 21, 2020 to December 31, 2022, in France, more than 155 million injections of COVID-19 vaccines were performed: more than 122 million injections with Comirnaty®, 24 million injections with Spikevax®, 7 million injections with Vaxzevria®, 1 million injections with Jcovden® and more than 37,000 injections with Nuvaxovid®. Vidprevtyn® and Bimervax® were not used in France during this period. In total, 190,000 cases of adverse event following immunization reports (25% serious, 75% non-serious) were documented, analyzed and recorded in the French national pharmacovigilance database by the 30 Regional Pharmacovigilance Centres: 124,647 cases (26% serious, 74% non-serious) with Comirnaty®, 33,115 cases (20% serious, 80% non-serious) with Spikevax®, 31,391 cases (23% serious, 77% non-serious) with Vaxzevria®, 1723 cases (36% serious, 64% non-serious) with Jcovden® and 92 cases (25% serious, 75% non-serious) with Nuvaxovid® (Figs. 1 and 2). Due to their specific indications, the distribution of adverse event following immunizations by age groups differed between the different vaccines. For Comirnaty® and Spikevax®, the 30—49 age group was the most represented, with 42,606 (35%) and 14,166 (43%) of reported adverse event following immunizations, respectively. The $\geq$ 65 age group represented 30,498 (24%) and 7075 (22%), respectively. For Vaxzevria® and Jcovden®, the 50—64 age group was the most represented, with 12,175 (49%) and 952 (56%), respectively. The $\geq$ 65 age group represented 7735 (25%) and 544 (32%), respectively. For Nuvaxovid®, the 30—49 age group was the most represented with 48 (52%) of reported adverse event following immunizations. The $\geq$ 65 age group represented 14 (15%) of reported adverse event following immunizations (Fig. 3). A total of 845 adverse event following immuniza-

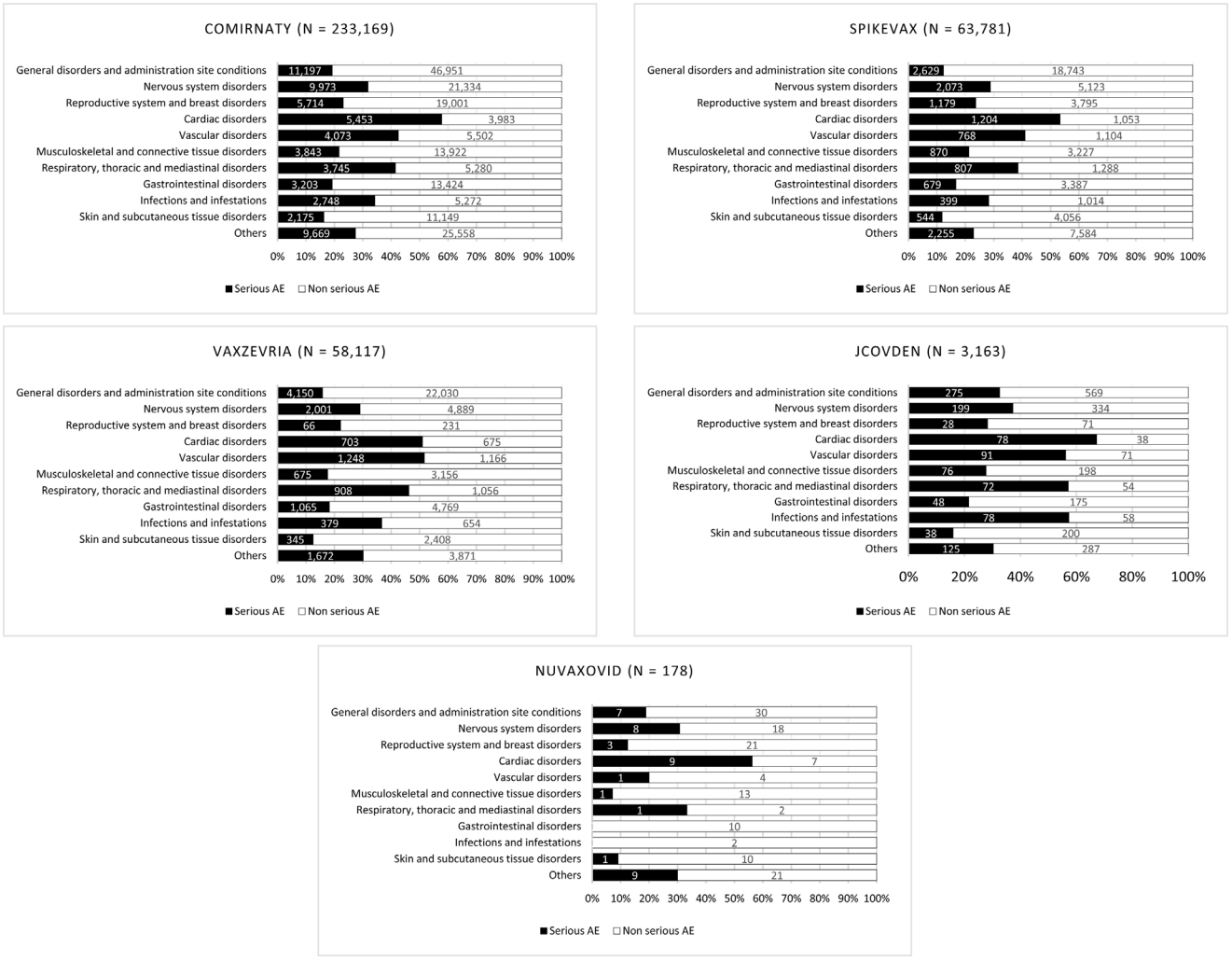

Figure 1. Numbers and seriousness of adverse event following immunizations reported in France organs with each COVID-19 vaccine.

tions have been reported in pregnant women, and 202 in breast-feeding women.

After expertise of the 190,000 cases of adverse event following immunization, the Regional Pharmacovigilance Centres identified and transmitted to the ANSM 1153 ''remarkable reports'' related to the vaccines. Eighty-two were retained by the experts and the monitoring committee as potential safety signals, and 53 were escalated to the PRAC for confrontation with other EU pharmacovigilance reports and collective discussion with all PRAC members. From these, 13 have been confirmed by the EMA and added to the summary of product characteristics of these vaccines (Table 1). Among them, some signals were specific to a type of vaccine (or ARNm) such as major flu-like syndrome, facial paralysis and Guillain-Barre syndrome or thrombosis associated with thrombocytopenia for adenovirus-based vaccines (for Vaxzevria® and Jcovden®), heavy menstrual bleeding for ARNm (Comirnaty® and Spikevax®), whereas others were reported for multiple type of vaccines, such as myocarditis/pericarditis for Comirnaty®, Spikevax® and Nuvaxovid®. Twenty-four safety signals are still under investigation such as hearing loss for mRNA vaccines and 16 are currently considered only for surveillance. Since the beginning of the enhanced national pharmacovigilance system in December 2022, there were 104 expert reports provided by Regional Pharmacovigilance Centres, 55 collegial meetings, and 59 web communications organized and prepared by ANSM.

Lessons learnt

The COVID-19 pandemic served as a true game changer with rapid implementation of efficacious new vaccines in the general population. Those vaccines against COVID-19 targeted first the elderly and adult population and were later introduced to adolescents and children [11—13].

For pharmacovigilance, before the COVID-19 crisis, around 40,000 adverse event following immunization per year were notified to Regional Pharmacovigilance Centres Network and recorded in the French national pharmacovigilance database for all marketed medicines, including vaccines. Within two years, for the COVID-19 vaccines only, more than 190,000 adverse event following immunization were reported, assessed and registered that contributed to following those vaccines' safety profile [14]. For local and systemic reactogenicity, more than 80% were non-serious,

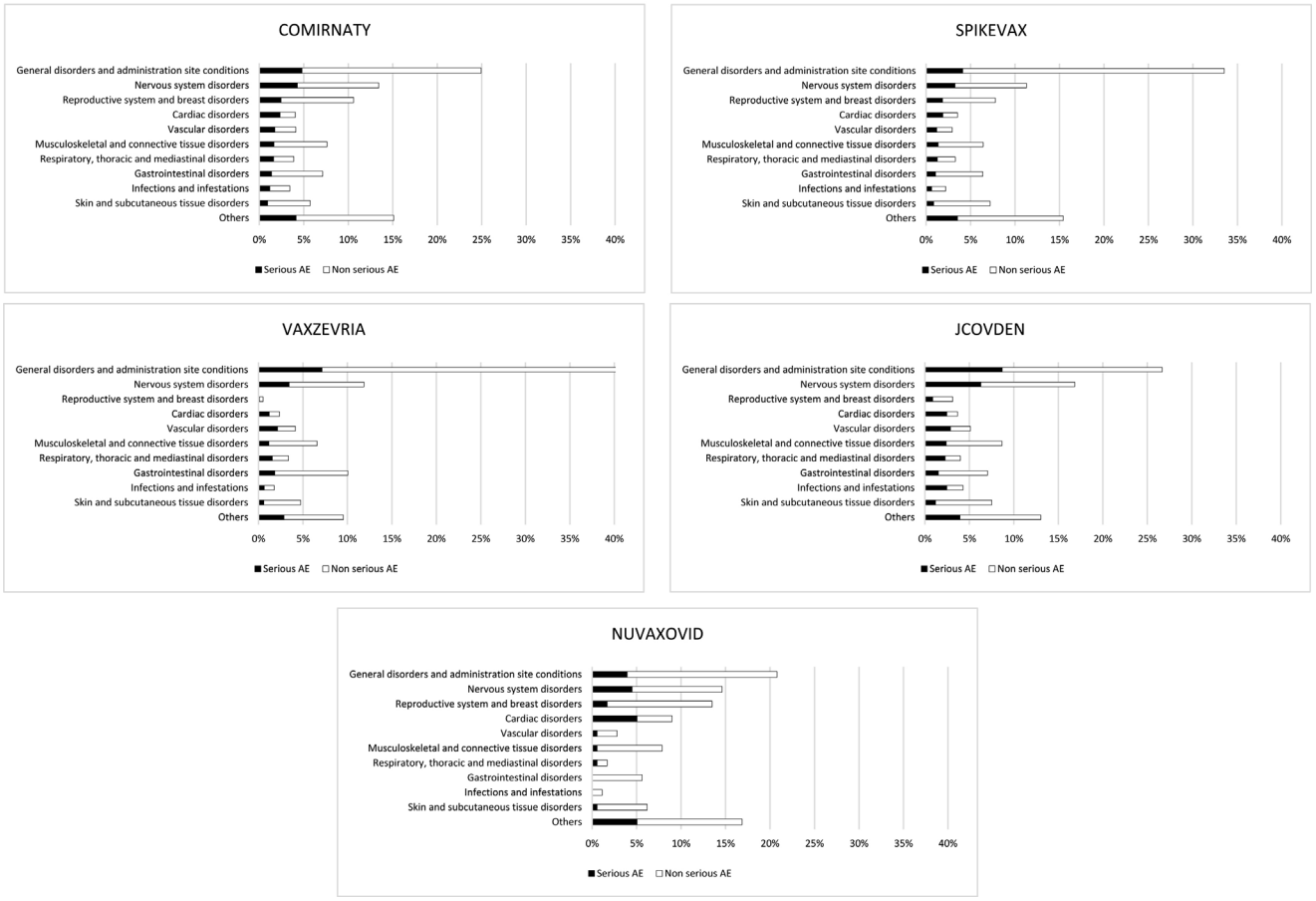

Figure 2. Percentage of adverse event following immunizations by organs and seriousness according to each COVID-19 vaccine.

and the vast majority were spontaneously resolved, with some differences between these six vaccines: more frequent local reactions for Spikevax® and more frequent systemic reactions for Vaxzevria® being more reactogenic.

The other adverse event following immunizations had differences due to populations of different ages and their mechanisms of action. In the initial introduction of the COVID-19 vaccines, Vaxzevria® and Jcovden® were used more widely in population over 50 years of age with specific adverse event following immunization, i.e. vascular disorders, such as thrombosis associated with thrombocytopenia [6], capillary leak syndrome and venous thromboembolism [15]. Conversely, Comirnaty® and Spikevax® vaccines, that were the only vaccines used in children and adolescents and were highly predominant in young adults, had a proportionally higher incidence of reporting of menstrual disorders in women, and of myocarditis and pericarditis than Vaxzevria® and Jcovden® [16—19].

Notably, signal detection ($n = 53$) at a national level, adjudication at the European level, communication to the public and to the scientific community, and translation into updated vaccine recommendation were highly coordinated [20—22]. For instance, the safety signal for myocarditis/pericarditis with mRNA vaccines was detected in France at the end of April 2021. By early June 2021, a first recommendation on the ANSM website was published to warn the general public and healthcare professionals about this risk. In early November 2021, after an in-depth and detailed analysis of the cases of myocarditis/pericarditis reported with Spikevax®, the Regional Pharmacovigilance Centres further identified that this effect occurred more frequently in young adult (< 30 years) than with Comirnaty® [20]. This new signal was confirmed by a pharmacoepidemiological study [23]. A French national immunization technical advisory groups's recommendation was immediately published, specifying that only Comirnaty® should be used in patients under 30 years of age [24]. France was also one of the main contributors to the European analysis of the heavy menstrual bleeding signal with mRNA vaccines, leading the PRAC to validate this signal in October 2022 [25—27].

After two full years of COVID-19 vaccine use, the safety profile for 4 first vaccines is now well characterised [28—31]. However, some of the underlying mechanisms for some of those adverse effects are still to be better understood and that some safety signals are still under investigation at the national and European level (Table 1) [17,32,33]. This achievement was mainly due to the effective coordination by ANSM with the Regional Pharmacovigilance Centres Network [34] and with the pharmacovigilance system in other European member states working closely with the PRAC [35]. In addition, pharmacoepidemiologic studies could efficiently complement pharmacovigilance monitoring and assessments over the period by providing quantifications and characterization of risks for some of the raised signals [36]. In France,

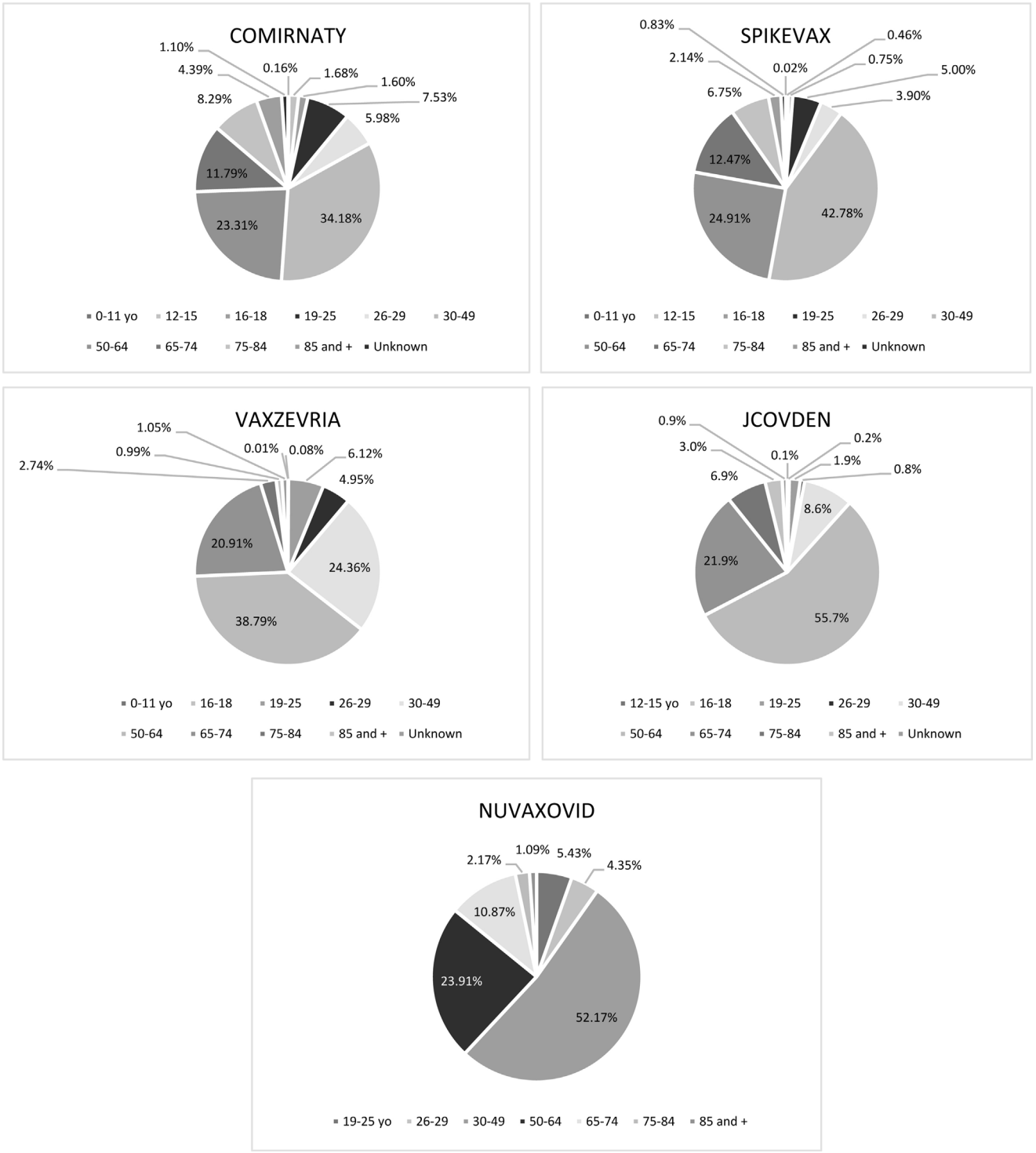

Figure 3. Adverse event following immunizations by age groups (years old, yo) according to each COVID-19 vaccine.

the role of Epi-Phare was key [37]. This scientific public entity is under the auspices of both ANSM and the French Health Insurance (''*Caisse nationale d'Assurance maladie*'', CNAM) [38] with permanent access to the French national health data system.

Among the remaining challenges and pitfalls, some of the adverse effects might have not been recognized promptly enough because they were not associated with severe symptoms from a medical point of view, but their impact on the quality of life needed to be taken into consideration. For instance, menstrual disorders [17,26] or hearing loss [39] which seriousness and impact involves a subjective dimension, were more difficult to assess.

To conclude on the lessons learnt, pharmacovigilance demonstrated once again its pivotal role in post-approval activities. This was even more highlighted during the moni-

Table 1 Safety signals detected by Regional Pharmacovigilance Centres network in France.

COMIRNATY	SPIKEVAX	VAXZEVRIA	JCOVDEN	NUVAXOVID
Confirmed by EMA and added to SmPC				
Myocarditis/ pericarditis Heavy menstrual bleeding	Myocarditis/ pericarditis Heavy menstrual bleeding Delay reactogenicity erythema multiform	Guillain-Barré syndrome Facial paralysis Influenza-like illness Thrombosis with thrombocytopenia Syndrome Hypersentivity	Thrombosis with thrombocytopenia Syndrome	Myocarditis/pericarditis
Under investigations at the national level				
Parsonage-Turner Syndrome Acquired haemophilia Auto-immune hepatitis Hearing loss Rheumatoid arthritis Menstrual disorders (except for cases of heavy menstrual bleeding)	Parsonage-Turner Syndrome Acquired haemophilia Auto-immune hepatitis Hearing loss Vasculitis Auto-immune haemolytic anaemia Menstrual disorders (except for cases of heavy menstrual bleeding)	Systemic necrotizing vasculitis[a] Menstrual disorders[a] Viral reactivation[a] Myocarditis/pericarditis[a] Hearing loss[a] Sarcoidosis[a] Thromboembolic event[a] Polymyalgia rheumatic[a]	Herpes Zoster[a]	Hearing loss Menstrual disorders

EMA: European Medicines Agency; SmPC: summary of product characteristics.
[a] Vaxzevria and Jcovden vaccines are no longer recommended in France, new adverse event following immunizations are expected to be few.

toring of the vaccination campaign that it was the only source of rapid signal identification, later confirmed by pharmacoepidemiologic studies after at best weeks, more often months. The enhanced national PV system also confirmed the complementarity between pharmacovigilance and pharmacoepidemiology and the need for an agile and adaptative approach to ensure a continued benefit/risk monitoring for its efficiency.

Disclosure of interest

The authors declare that they have no competing interest.

Références

[1] European Medicines Agency. In: COVID-19 guidance: evaluation and marketing authorization; 2023 [Accessed 8 November 2024] https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/guidance-developers-companies/covid-19-guidance-evaluation-marketing-authorisation.

[2] ANSM. In: La surveillance renforcée des medicaments; 2023 [Accessed 8 November 2024] https://ansm.sante.fr/page/la-surveillance-renforcee-des-medicaments.

[3] Jonville-Bera AP, Gautier S, Micallef J, Massy N, Atzenhoffer M, Grandvuillemin A, et al. Monitoring the safety of drugs and COVID-19 vaccines by the French Pharmacovigilance Centers during the pandemic: a win-win bet with Health Authorities! Therapie 2023;78:467—75.

[4] Lacroix C, Salvo F, Gras-Champel V, Gautier S, Massy N, Valnet-Rabier MB, et al. French organization for the pharmacovigilance of COVID-19 vaccines: a major challenge. Therapie 2021;76:297—303.

[5] Benkebil M, Gautier S, Gras-Champel V, Massy N, Micallef J, Valnet-Rabier MB. COVID-19 vaccines surveillance in France: a global response to a major national challenge. Anaesth Crit Care Pain Med 2021;40:100866.

[6] Gras-Champel V, Liabeuf S, Baud M, Albucher JF, Benkebil M, Boulay C, et al. Atypical thrombosis associated with VaxZevria® (AstraZeneca) vaccine: data from the French Network of Regional Pharmacovigilance Centres. Therapie 2021;76:369—73.

[7] ANSM. In: Lancement de la nouvelle application nationale de pharmacovigilance; 2021 [Accessed 8 November 2024] https://ansm.sante.fr/actualites/lancement-de-la-nouvelle-application-nationale-de-pharmacovigilance.

[8] EMA. In: Eudravigilance system overview; 2016 [Accessed 8 november 2024] https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance/eudravigilance-system-overview.

[9] EMA. In: Work instructions. EPITT user registration and management—Assessment of eligibility for an EPITT account; 2016 [Accessed 8 November 2024 (3 pp.)] https://www.ema.europa.eu/en/documents/win/work-instructions-european-pharmacovigilance-issues-tracking-tool-epitt-user-registration-management_en.pdf.

[10] ANSM. In: Point de situation sur la surveillance des vaccins contre le Covid-19—Période du 22/12/2022 au 19/01/2023; 2023 [Accessed 8 november 2024] https://ansm.

sante.fr/actualites/point-de-situation-sur-la-surveillance-des-vaccins-contre-la-covid-19-periode-du-22-12-2022-au-19-01-2023.
[11] HAS. In: Stratégie de vaccination contre le Sars-Cov-2 - Recommandation relative à la vaccination contre la Covid-19 de l'entourage de certaines populations vulnérables - synthèse des données relatives à l'efficacité des vaccins contre la Covid-19 sur la transmission du SARS-COV-2 au 1er avril 2021; 2021 [Accessed 8 november 2024] https://www.has-sante.fr/jcms/p_3264090/fr/strategie-de-vaccination-contre-le-sars-cov-2-recommandation-relative-a-la-vaccination-contre-la-covid-19-de-l-entourage-de-certaines-populations-vulnerables-synthese-des-donnees-relatives-a-l-efficacite-des-vaccins-contre-la-covid-19-sur-la-transmission-du-sars-cov-2-au-1er-avril-2021.
[12] HAS. In: Stratégie de vaccination contre la Covid-19—Place du vaccin à ARNm COMIRNATY® chez les 5—11 ans; 2021 [Accessed 8 November 2024] https://www.has-sante.fr/jcms/p_3306504/fr/strategie-de-vaccination-contre-la-covid-19-place-du-vaccin-a-arnm-comirnaty-chez-les-5-11-ans.
[13] EMA. In: COVID-19 medicines; 2023 [Accessed 8 November 2024] https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/covid-19-vaccines-authorised#originally-authorised-covid-19-vaccines-section.
[14] ANSM. Effets indésirables des vaccins contre le Covid-19. In: Données de pharmacovigilance; 2023, assessed as of 21 August 2023. [Accessed 8 November 2024] https://ansm.sante.fr/dossiers-thematiques/covid-19-suivi-hebdomadaire-des-cas-deffets-indesirables-des-vaccins.
[15] Massy N, Atzenhoffer M, Boulay C, Pecquet PE, Ledys F, Cracowski JL, et al. COVID-19 and adenovirus vaccines: French experience of enhanced pharmacovigilance. Therapie 2023;78:489—98.
[16] Salvo F, Pariente A, Valnet-Rabier MB, Drici M, Cholle C, Mathieu C, et al. Role of spontaneous reporting in investigating the relationship between mRNA COVID-19 vaccines and myocarditis: the French perspective. Therapie 2023;78:509—15.
[17] Valnet-Rabier MB, Tebacher M, Gautier S, Micallef J, Salvo F, Pariente A, et al. Pharmacovigilance signals from active surveillance of mRNA platform vaccines (tozinameran and elasomeran). Therapie 2023;78:499—507.
[18] Foltran D, Delmas C, Flumian C, De Paoli P, Salvo F, Gautier S, et al. Myocarditis and pericarditis in adolescents after first and second doses of mRNA COVID-19 vaccines. Eur Heart J Qual Care Clin Outcomes 2022;8:99—103.
[19] Chouchana L, Blet A, Al-Khalaf M, Kafil T, Nair G, Robblee J, et al. Features of inflammatory heart reactions following mRNA COVID-19 vaccination at a global level. Clin Pharmacol Ther 2022;111:605—13.
[20] Crommelynck S, Thill P. Pharmacovigilance for COVID-19 vaccines: a 1-year experience in France. Infect Dis Now 2022;52:S16—8.
[21] HAS. In: Vaccination dans le cadre de la COVID 19; 2024 [Accessed 8 november 2024] https://has-sante.fr/jcms/p_3178533/fr/vaccination-dans-le-cadre-de-la-covid-19-les-actions-de-la-has.
[22] HAS. Vaccination dans le contexte du Covid-19 - Les actions de la HAS. In: Recommandation vaccinale; 2020 [Accessed 8 November 2024] https://www.has-sante.fr/jcms/p_3186124/fr/vaccination-dans-le-contexte-du-covid-19-les-actions-de-la-has.
[23] Le Vu S, Bertrand M, Jabagi MJ, Botton J, Drouin J, Baricault B, et al. Age and sex-specific risks of myocarditis and pericarditis following Covid-19 messenger RNA Vaccines: a nationwide assessment. Nat Commun 2022;13:3633.
[24] HAS. In: Covid-19 : la HAS précise la place de Spikevax® dans la stratégie vaccinale; 2021 [Accessed 8 november 2024] https://www.has-sante.fr/jcms/p_3297260/fr/covid-19-la-has-precise-la-place-de-spikevax-dans-la-strategie-vaccinale.
[25] Al Kadri HM, Al Sudairy AA, Alangari AS, Al Khateeb B, El-Metwally A. COVID-19 vaccination and menstrual disorders among women: findings from a meta-analysis study. J Infect Public Health 2023;16:697—704.
[26] Duijster JW, Schoep ME, Nieboer BTE, Jajou R, Kant A, Van Hunsel F. Menstrual abnormalities after COVID-19 vaccination in the Netherlands: a description of spontaneous and longitudinal patient-reported data. Br J Clin Pharmacol 2023;89:3126—38.
[27] EMA. In: Signal assessment on heavy menstrual bleeding with COVID-19 mRNA vaccine (Spikevax); 2022 [Accessed 8 November 2024 (64 pp.)] https://www.ema.europa.eu/en/documents/prac-recommendation/signal-assessment-heavy-menstrual-bleeding-covid-19-mrna-vaccine-spikevax_en.pdf.
[28] EMA. In: Comirnaty SmPC; 2023 [Accessed 8 November 2024 (706 pp.)] https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf.
[29] EMA. In: Spikevax SmPC; 2023 [Accessed 8 November 2024 (270 pp.)] https://www.ema.europa.eu/en/documents/product-information/spikevax-previously-covid-19-vaccine-moderna-epar-product-information_en.pdf.
[30] EMA. In: Jcovden SmPC; 2023 [Accessed 8 November 2024 (41 pp.)] https://www.ema.europa.eu/en/documents/product-information/jcovden-previously-covid-19-vaccine-janssen-epar-product-information_en.pdf.
[31] EMA. In: Vaxzevria SmPC; 2021 [Accessed 8 November 2024] https://www.ema.europa.eu/en/medicines/human/EPAR/vaxzevria#product-information-section.
[32] Ramdani Y, Largeau B, Jonville-Bera AP, Maillot F, Audemard-Verger A. COVID-19 vaccination as a trigger of IgA vasculitis: a global pharmacovigilance study. J Rheumatol 2023;50:564—7.
[33] Fillon A, Sautenet B, Barbet C, Moret L, Thillard EM, Jonville-Bera AP, et al. De novo and relapsing necrotizing vasculitis after COVID-19 vaccination. Clinical Kidney 2021;15:560—3.
[34] ANSM. In: Surveillance de la campagne vaccinale contre le Covid-19; 2021 [Accessed 8 November 2024] https://ansm.sante.fr/dossiers-thematiques/covid-19-vaccins/covid-19-dispositif-de-surveillance-renforcee-des-vaccins.
[35] EMA. In: Safety of COVID-19 vaccines; 2023 [Accessed 8 November 2024] https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/safety-covid-19-vaccines#how-ema-monitors-vaccine-safety-section.
[36] Pottegard A, Lund LC, Karstad O, Dahl J, Andersen M, Hallas J, et al. Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population based cohort study. BMJ 2021;373:n1114.
[37] EpiPhare. In: Surveillance pharmaco-épidémiologique des vaccins; 2024 [Accessed 8 November 2024] https://www.epi-phare.fr/surveillance-pharmaco-epidemiologique-des-vaccins/.
[38] EpiPhare. 2024 https://www.epi-phare.fr/en/ [Accessed 8 November 2024].
[39] Thai-Van H, Valnet-Rabier MB, Anciaux M, Lambert A, Maurier A, Cottin J, et al. Safety signal generation for sudden sensorineural hearing loss following messenger RNA COVID-19 vaccination: postmarketing surveillance using the French Pharmacovigilance Spontaneous Reporting Database. JMIR Public Health Surveill 2023;9:e45263.