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COVID-19/PHARMACOEPIDEMIOLOGY

Evaluation of Covid-19 vaccines: Pharmacoepidemiological aspects

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Summary The marketing authorization granted to SARS-Cov-2 vaccines was accompanied by reinforced safety monitoring plans. These plans' implementation was part of the usual logic of post-marketing surveillance of new and innovative health products. It was especially adapted to the context of post-marketing monitoring of drugs developed according to the usual scientific quality standards but in an accelerated schedule. In Europe, the reinforced surveillance system relies on the complementary strengths of pharmacovigilance and pharmacoepidemiology. If the performances of pharmacovigilance monitoring are incomparable for the detection of safety signals relating to rare events of atypical presentation, it needs to be completed with pharmacoepidemiology activities for more common events, either multifactorial or frequently classified as idiopathic. The pharmacoepidemiological monitoring developed in Europe was elaborated before the first SARS-Cov-2 vaccines where marketed, taking into account the lessons learned from the vaccination campaign against 2009 A (H1N1) influenza. It includes numerous academic studies as well as studies performed within vaccines risk management plans. In terms of safety, those defined a priori mostly concerns a list of pre-established health events of specific interest. Aside of these planned activities, ad-hoc studies will be latter developed on purpose to investigate safety signals or potential signals that could be identified as the result of pharmacovigilance activities. Aside of these regulated activities, as for today, very few studies have been published regarding SARS-Cov-2 vaccines; most of the existing consist in preprints that should be considered with caution. Pharmacoepidemiology of vaccines is thought to allow near-real time monitoring that needs sufficient time to provide with valid results. In the

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constant urge for information that accompanies COVID-related science, it is important not to make haste the enemy of speed and to let pharmacoepidemiology provides with what it is expected to do: rock-solid scientific information contributing to evidence-based decision-making.

Abbreviations

ACCESS vACCine covid-19 monitoring readinESS
AESI adverse event of specific interest
CNAM French Health Insurance (*Caisse nationale de l'Assurance maladie*)
COVID-19 coronavirus disease 2019
EMA European Medicines Agency
ENCEPP EMA European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
FDA Food and Drug Administration
GIS EPIPHARE *Groupement d'intérêtspécifique* EPI-PHARE
mRNA messenger RNA
RMP risk management plan
SARS CoV-2 severe acute respiratory syndrome coronavirus 2
SPEAC Safety Platform for Emergency vACcines

Introduction

The marketing authorization granted to vaccines indicated for the prevention of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and severe infection was accompanied by reinforced safety monitoring plans. These concerns the four vaccines currently authorized in the European Union, two mRNA vaccines (the Pfizer-BioNTech Comirnaty® and the Moderna® SARS-CoV-2 messenger RNA [mRNA]-1273 vaccine) and two adenovirus-vector based vaccines (the Oxford AstraZeneca Vaxzevria® and the Janssen COVID-19 Ad26.COV2-S [recombinant] vaccine).

The implementation of these enhanced measures was part of the usual logic of post-marketing surveillance of new health products, particularly innovative ones. It was also especially adapted to the context of post-marketing monitoring of drugs developed according to the usual scientific standards of quality but in an accelerated schedule, a context likely to increase the mistrust specifically linked to vaccines in the population.

In Europe, the reinforced surveillance system in place relies on the complementary strengths of pharmacovigilance and pharmacoepidemiology.

For the early identification of safety signals, the performance of pharmacovigilance and the analysis of spontaneous reporting databases are unequalled to date [1]. From a limited number of very unusual cases, pharmacovigilance activity can allow detecting very quickly safety signals relating to adverse effects not previously identified during preclinical or clinical studies including large phase III randomized clinical trials. This ability to rapidly spot such safety signals is due to the extraordinary surveillance capacity of the globalized pharmacovigilance system to which each country or group of countries contributes.

In the case of France, as detailed in the article by Micallef et al., the cases reported continuously to the system are analyzed daily by the Regional Pharmacovigilance Centers [2]. The results of this medico-pharmacological analysis, together with the information on the case that is completed whenever necessary by a return to the reporter, are also transmitted daily to the National Pharmacovigilance Database. Shared at the European level, this information and the synthesis of the expertise that is carried out each week allows for the detection of safety signals in real time, the only limits of which are linked to: 1- the analysis and processing capacities (in terms of human resources), 2- the frequency of occurrence and notification of adverse events (also relating to the rhythm of the vaccination campaigns and the number of vaccinated subjects), and 3- the possibility of identifying cases with an atypical presentation.

The rapid identification in the European Union of AstraZeneca vaccine Vaxzevria® adverse reactions consisting in venous thromboembolism of atypical locations, whether or not accompanied by thrombocytopenia, is a perfect illustration of the capabilities and strength of this activity [3]. It is also a perfect example of the type of events for which these capacities are maximal: rare events of atypical presentation.

The limits of the detection of safety signals based on the pharmacovigilance clinical and pharmacological analysis of individual cases are, on the other hand, marked when it comes to events of common occurrence in the population and which presentation in the reported cases does not present any particular specificity. In this case they are even more important for common events which are generally of multifactorial origin [4]. It is also limited for events that can be less frequent but for which the etiological research is often negative and for which a conclusion of idiopathic origin is common in the current state of knowledge.

For these events, the pharmacovigilance analysis must be completed by a pharmacoepidemiological analysis [5,6]. However, this analysis cannot be general and extended to all events, as is the case for pharmacovigilance. This is because it is not based on a generalized system, with spe-

cific resources, and shared between countries, which would ensure a permanent data watch. And because the data sources that it can use are not adapted to the study of all types of effects.

For these reasons, the pharmacoepidemiological surveillance of vaccines indicated for the prevention of coronavirus disease 2019 (COVID-19) infection is necessarily targeted. For these reasons also, it is necessarily delayed in time compared to the pharmacovigilance evaluation. At best, pharmacoepidemiological assessment of vaccines can thus consist in near-real time evaluation [7].

These characteristics explain the modalities chosen for the pharmacoepidemiological surveillance of vaccines indicated for the prevention of COVID-19 infection, which are latter detailed. These modalities have been elaborated by regulators considering the lessons learned from the last worldwide mass vaccination campaign performed during the 2009 A (H1N1) influenza virus pandemic for which delays could be prolonged between the emerging of an interrogation and the final pharmacoepidemiological answer that could be provided, as it was the case for narcolepsy [8—10].

Pharmacoepidemiological strategies and planned activities for SARS-CoV-2 vaccine monitoring

In order to allow the near-real time pharmacoepidemiological evaluation of SARS-CoV-2 vaccines to provide with some results as early as possible, an important common monitoring plan has been developed for all vaccines to be marketed in this indication in Europe.

This focuses on a list of health events of specific interests, determined with regards to the safety issues or questions that can have concerned existing vaccines indicated for the prevention of other diseases and with regards to health events constituting specific complications of SARS-CoV-2 infections.

The list of these adverse events of specific interests has been defined by the Safety Platform for Emergency vACcines (SPEAC) and the Brighton Collaboration, and was completed in Europe with additional events. It initially included enhanced disease following immunization, multisystem inflammatory syndrome in children, acute respiratory distress syndrome, acute cardiovascular injury, coagulation disorder, acute kidney injury, acute liver injury, generalized convulsion, Guillain-Barré syndrome, meningoencephalitis, acute disseminated encephalomyelitis, anosmia and dysgueusia, chilblain—like lesions, single organ cutaneous vasculitis, multiform erythema, anaphylaxis, acute aseptic arthritis, thrombocytopenia. It was completed in Europe with narcolepsy, transverse myelitis and events relating to pregnancy outcome (preterm birth, major congenital anomalies, microcephaly, fetal growth restriction, gestational diabetes, preeclampsia, termination of pregnancy for fetal anomaly, neonatal death, and spontaneous abortions and stillbirth).

In Europe, the European Medicines Agency (EMA) contracted with the vACCine covid-19 monitoring readinESS (ACCESS) consortia [11], coordinated by the Utrecht University, to conduct the pharmacoepidemiological monitoring of the COVID vaccines. The developed monitoring plan comprises:

- activities allowing to determine baseline incidence rates;
- activities allowing to assess the effectiveness of COVID-19 vaccines in preventing hospitalizations for COVID-19 and mortality due to COVID-19;
- activities allowing to monitor and assess the safety of COVID vaccines in real-life setting.

These includes first field cohort studies with solicited adverse event reporting aiming to assess the incidence of adverse events in vaccinated subjects. Noticeably, the European study there used common procedures elaborated disregarding the informatics infrastructure of pharmacovigilance systems. This will potentially be responsible for pharmacovigilance overload as the solicited reporting is likely to retrieve an important amount of common side effects (e.g. reactogenicity, headache, nausea) of no interest for signal detection, little interest for safety monitoring, and high treatment burden for pharmacovigilance systems which will have to treat these data as any other report.

Aside of these, these mostly include study performed through the secondary use of electronic healthcare databases (German, Dutch, Danish, Spanish, Italian, British, Norwegian, and French). In those, detection analyses will be run in first step, which results will be enriched by rapid assessments using ecological or self-control risk interval methods, before ad-hoc studies are performed if needed to confirm/finally quantified risk increase and associations.

Similar activities including rapid cycle analyses and ulterior ad-hoc studies investigating specific safety signals are planned by the US Food and Drug Administration (FDA) in the context of the Sentinel Network activities.

Finally, national regulators also have scheduled some pharmacoepidemiological activities, as it is the case in France through the ''*Groupement d'Intérêt Spécifique* EPI-PHARE'' (GIS EPI-PHARE), a joint structure from the French ANSM and the French Health Insurance (CNAM). Only its general action programme (SARS-Cov-2 vaccine monitoring) is known to date [12]. These activities are notably facilitated by the collection of specific national data regarding vaccines, COVID hospitalizations and COVID screening tests in addition to the usual health care reimbursement collected data, which will be soon made accessible to all researchers by the French Health Data Hub.

In addition to the regulators actions, the risk management plans accompanying marketing authorization also include some specific pharmacoepidemiological studies to be led by the pharmaceutical companies [13—16].

The Comirnaty® Pfizer-BioNTech risk management plan thus includes four non-interventional studies to be performed from. These comprise three secondary databases analyses aimed at estimating incidence rates of safety events of interest, one in a cohort of US active military and their families, one in a cohort of US veterans, and one in a cohort of COVID-19 vaccinated subjects in the EU, and a field cohort study of vaccinated EU citizens which will monitor the safety of the vaccine in real-world setting. Similar studies are comprised in the Vaxzevria® Oxford AstraZeneca vaccine risk management plan, which includes a pregnancy subcohort, and which planned secondary health data sources studies both aims at assessing baseline incidences and

estimating relative risk of safety concerns including adverse event of specific interest (AESIs) among all populations targeted for vaccination and in specific populations as in patient with immunodeficiency or treated with immunosuppressants. The Moderna® SARS-CoV-2 mRNA-1273 vaccine risk management plan also includes a pregnancy study and pharmacoepidemiological studies aiming to provide AESIs incidence as well as association estimates using US and EU secondary datasources.

Finally, all vaccines risk management plan (RMP) additionally include studies aiming to evaluate the effectiveness of the vaccines in real-world setting.

Pharmacoepidemiological data and publication regarding SARS-CoV-2 vaccines monitoring

As of 2021 May the 10th, very rare publications have been done regarding these vaccines. The earlier one consisted in a study of vaccine hesitancy [17]. The first available pharmacoepidemiology data concerned Israel, which vaccinated rapidly and massively. Dagan, et al. were thus able to quickly confirm experimental data regarding the effectiveness of Comirnaty® Pfizer-BioNTech vaccine in population by using Israel's health care organization data for almost 600,000 vaccinated subjects [18]. Indeed, Israel is today the country with the largest cohort of patients fully vaccinated with two doses of Comirnaty® Pfizer-BioNTech vaccine (72% of the 6.5 million people on April 3, 2021) allowing to highlight the effectiveness in preventing SARS-CoV-2 infections and COVID-19-related hospitalizations, severe disease, or death [19].

In the following, researchers from Scotland associated with the Scottish Health Insurance have released data from a similar study demonstrating the effectiveness of a first-dose of Comirnaty® Pfizer-BioNTech or Vaxzevria® Oxford AstraZeneca vaccines [20]. More recently, an observed to expected study was published analyzing the possibility that the reporting of venous thrombosis with Vaxzevria® Oxford-AstraZeneca vaccine would be coincidental [21]. The latter appeared to provide an answer to a question that did not correspond to the interrogation existing at that time, that already targeted specific uncommon venous thrombosis and not any venous thrombosis. Focusing on a much larger group of events was thus heavily at risk of conveying a dilution bias. Additionally, as always for such analyses, it needed to warn strongly against results that compare expected based on incidence data, and observed based on reporting ones. For such type of analyses, as reporting is not meant to reflect incidences, negative results are so often the rule that they should always be considered with caution.

Finally, as usual since the start of the COVID pandemic, some publications have arisen that did not go through the peer-review process to date.

This is both the case for the AESI incidence estimate results provided by the ACCESS and the OHDSI consortia, the first of which can be accessed through the EMA European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCEPP) [22], and the second on the now well-known preprint Medrxiv platform [23].

Additionally, and very lately, a study was published by Oxford researchers that compared the risk of venous cerebral thrombosis in patients vaccinated with mRNA vaccines and in patients infected with SARS-CoV-2 [24]. Using a different datasource, the authors completed their investigation by evaluating also the risk for patients vaccinated with Vaxzevria®. Many comments can be made regarding this study, the first of which questioning the relevancy of comparing the risk of such events in healthy vaccinated vs. infected. The very recent publication on Nationwide healthcare registers in Denmark and Norway could constitute the perfect counter-example, both in term of methodological robustness and in term of compliance to the peer-review process [25]. This study showed increased rates of venous thromboembolic events, including cerebral venous thrombosis, with Vaxzevria® vaccine. The authors highlighted and remind that these events, which remain rare, should be contrasted with the proven beneficial effects of the vaccination.

Let's hope here that preprints and non-validated results will not turn deleterious. No one will disagree that near-real time monitoring and early pharmacoepidemiological results are of utmost need in the context of SARS-CoV-2 vaccine surveillance. But to be more accurate, the real need is of pharmacoepidemiological valid results. In the context where vaccination is of such importance, and trust in vaccines is always frail, validity and methodological compromises should never be the price to pay for earlier results. This is partly what led to hydroxychloroquine false hopes, this must not be what would compromise the true ones SARS-CoV-2 vaccines are.

Conclusion

A tremendous effort of pharmacoepidemiological monitoring has been developed to accompany and complete pharmacovigilance activities in the context of the enforced surveillance systems implemented for SARS-CoV-2 vaccines. Most of it has been carefully planned and prepared to allow these real-time monitoring activities, the first results of which have already been make public but did not go through peer-review.

A former EMA Pharmacovigilance Risk Assessment Committee chair used to wisely say ''Let's not better be the enemy of good''. In the context of SARS-CoV-2 monitoring, the publication of its results, and the urge for information both arising from the publics and the politics, it would also be wise to give pharmacoepidemiology science the times it need to provide with valid results concerning SARS-CoV-2 vaccines, and not to make haste the enemy of speed.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Patadia VK, Schuemie MJ, Coloma P, Herings R, van der Lei J, Straus S, et al. Evaluating performance of electronic

healthcare records and spontaneous reporting data in drug safety signal detection. Int J Clin Pharm 2015;37:94—104.
[2] Lacroix C, Salvo F, Gras-Champel V, Gautier S, Massy N, Valnet-Rabier MB, et al. French organization for the Pharmacovigilance of vaccines for COVID-19: a major challenge. Therapie 2021, http://dx.doi.org/10.1016/j.therap.2021.05.003. S0040-5957(21)00126-8. https://www.em-consulte.com/article/1449516/french-organization-for-the-pharmacovigilance-of-c. [Accessed 29 May 2021].
[3] Agence nationale de sécurité du médicament et des produits de santé. Point de situation sur la surveillance des vaccins contre la COVID-19 - Période du 12/03/2021 au 18/03/2021; 2021, https://ansm.sante.fr/actualites/point-de-situation-sur-la-surveillance-des-vaccins-contre-la-covid-19-periode-du-12-03-2021-au-18-03-2021. [Accessed 10 May 2021].
[4] Pacurariu AC, Straus SM, Trifirò G, Schuemie MJ, Gini R, Herings R, et al. Useful interplay between spontaneous ADR reports and electronic healthcare records in signal detection. Drug Saf 2015;38:1201—10.
[5] Faillie JL, Montastruc F, Montastruc JL, Pariente A. Pharmacoepidemiology and its input to pharmacovigilance. Therapie 2016;71:211—6.
[6] Sommet A, Pariente A. Methods in pharmacoepidemiology. Therapie 2019;74:187—97.
[7] Leite A, Andrews NJ, Thomas SL. Assessing recording delays in general practice records to inform near real-time vaccine safety surveillance using the Clinical Practice Research Datalink (CPRD). Pharmacoepidemiol Drug Saf 2017;26:437—45.
[8] Dauvilliers Y, Arnulf I, Lecendreux M, Monaca Charley C, Franco P, Drouot X, et al. Increased risk of narcolepsy in children and adults after pandemic H1N1 vaccination in France. Brain 2013;136(Pt 8):2486—96.
[9] European Center for Disease Prevention and Control. Narcolepsy in association with pandemic influenza vaccinationA multi-country European epidemiological investigation - Technical report; 2012, https://www.ecdc.europa.eu/sites/default/files/documents/ECDC%202012%20VAESCO%20Narco%20report%20FULL.pdf. [Accessed 10 May 2021 (164 pp.)].
[10] European Medicines Agency. Questions and answers on the review of Pandemrix Influenza vaccine (H1N1) (split virion, inactivated, adjuvanted) A/California/7/2009 (H1N1)v like strain (X-179A) Outcome of a procedure under Article 20 of Regulation (EC) No 726/2004; 2011, https://www.ema.europa.eu/en/documents/medicine-qa/questions-answers-review-pandemrix-influenza-vaccine-h1n1-split-virion-inactivated-adjuvanted/california/7/2009-h1n1v-strain-x-179a_en.pdf. [Accessed 10 May 2021 (3 pp.)].
[11] VAC4EU. COVID-19 vaccine monitoring; 2021, https://vac4eu.org/covid-19-vaccine-monitoring/. [Accessed 10 May 2021].
[12] GIS EPI-PHARE. Surveillance pharmaco-épidémiologique des vaccins contre la COVID-19; 2021, https://www.epi-phare.fr/actualites/surveillance-pharmaco-epidemiologique-des-vaccins-contre-la-covid-19/. [Accessed 10 May 2021].
[13] Pfizer-BioNTech. BNT162b2 COVID-19 mRNA vaccine risk management plan; 2021, https://www.ema.europa.eu/en/documents/rmp-summary/comirnaty-epar-risk-management-plan_en.pdf. [Accessed 10 May 2021 (115 pp.)].
[14] Janssen-Cilag International NV. European Union risk management plan VAC31518(Ad26.COV2.S); 2021, https://www.ema.europa.eu/en/documents/rmp-summary/covid-19-vaccine-janssen-epar-risk-management-plan_en.pdf. [Accessed 10 May 2021 (103 pp.)].
[15] AstraZeneca. European Union risk management plan (EU RMP) for COVID-19 vaccine Astrazeneca(ChAdOx1-S [Recombinant]); 2020, https://www.ema.europa.eu/en/documents/rmp-summary/vaxzevria-previously-covid-19-vaccine-astrazeneca-epar-risk-management-plan_en.pdf. [Accessed 10 May 2021 (106 pp.)].
[16] ModernaTX Inc. EU Risk Management Plan for COVID-19 Vaccine Moderna; 2021, https://www.ema.europa.eu/en/documents/rmp-summary/covid-19-vaccine-moderna-epar-risk-management-plan_en.pdf. [Accessed 10 May 2021 (95 pp.)].
[17] Ceulemans M, Foulon V, Panchaud A, Winterfeld U, Pomar L, Lambelet V, et al. Vaccine willingness and impact of the COVID-19 pandemic on women's perinatal experiences and practices-a multinational, cross-sectional study covering the first wave of the pandemic. Int J Environ Res Public Health 2021;18(7):3367.
[18] Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. N Engl J Med 2021:1412—23.
[19] Haas EJ, Angulo FJ, McLaughlin JM, Anis E, Singer SR, Khan F, et al. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. Lancet 2021;397(10287):1819—929, http://dx.doi.org/10.1016/S0140-6736(21)00947-8.
[20] Vasileiou E, Simpson CR, Robertson C, Shi T, Kerr S, Agrawall U, et al. Effectiveness of first dose of COVID-19 vaccines against hospital admissions in Scotland: national prospective cohort study of 5.4 million people. https://www.ed.ac.uk/files/atoms/files/scotland_firstvaccinedata_preprint.pdf. [Accessed 29 May 2021 (21 pp.)].
[21] Østergaard SD, Schmidt M, Horváth-Puhó E, Thomsen RW, Sørensen HT. Thromboembolism and the Oxford-AstraZeneca COVID-19 vaccine: side-effect or coincidence? Lancet 2021;397(10283):1441—3.
[22] Willame C, Sturkenboom M, Weibel D. Background rates of adverse events of special interest for monitoring COVID-19 vaccines; 2021, http://www.encepp.eu/documents/DraftReport.pdf. [Accessed 10 May 2021 (94 pp.)].
[23] Li X, Ostropolets A, Makadia R, Shaoibi A, Rao G, Sena AG, et al. Characterizing the incidence of adverse events of special interest for COVID-19 vaccines across eight countries: a multinational network cohort study; 2021, https://www.medrxiv.org/content/10.1101/2021.03.25.21254315v2.full. [Accessed 10 May 2021].
[24] Taquet M, Husain M, Geddes JR, Luciano S, Harrison P. Cerebral venous thrombosis: a retrospective cohort study of 513,284 confirmed COVID-19 cases and a comparison with 489,871 people receiving a COVID-19 mRNA vaccine; 2021, https://osf.io/a9jdq/ [Accessed 29 May 2021].
[25] Pottegård A, Lund LC, Karlstad Ø, 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].