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Original Article

PHARMACOVIGILANCE CHALLENGES OF COVID-19 VACCINE SAFETY MONITORING DURING THE PANDEMIC - A NARRATIVE REVIEW

Dagmara Mirowska-Guzel[1], Magdalena Niedzielko[*1], Barbara de Bernardi[2], Antonella Fretta[2], Marcin Kruk[3], Weronika Lepionka[3], Kavita Ramji[3], Patrick Caubel[4]

[1] *Department of Experimental and Clinical Pharmacology, Medical University of Warsaw, Banacha 1b, 02-097, Warsaw, Poland*

[2] *Worldwide Medical and Safety, Pfizer Italia srl, Via Anna Maria Mozzoni, 12, 20152 Milan, Italy*

[3] *Worldwide Medical and Safety, Pfizer Polska, Żwirki i Wigury 16b, 02-092, Warsaw, Poland*

[4] *Worldwide Medical and Safety, Pfizer Inc, 500 Arcola Rd Collegeville, Pennsylvania, United States*

* Correspondence, e-mail: magdalena.niedzielko@wum.edu.pl

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ABSTRACT

This article explores the challenges related to the immense workload associated with pharmacovigilance during the COVID-19 pandemic as well as strategies and solutions employed by key stakeholders, including regulators, industry, and academia. The rapid development and rollout of COVID-19 vaccines was accompanied by increased public interest in their safety, resulting in the collection and analysis of an unprecedented volume of safety data. Requests from regulators worldwide for the accelerated preparation and submission of aggregate safety reports, as well as ad hoc data requests, presented additional challenges. The academic community voluntarily contributed by summarizing emerging evidence on vaccine safety, conducting research to clarify potential mechanisms underlying adverse events, and examining factors associated with vaccine hesitancy. An effective pharmacovigilance system played a crucial role in gathering and rapidly analyzing large amounts of data to identify signals, refine the safety profile of a new medicinal product, and respond promptly to any emerging concerns to ensure that patients are not exposed to medications with an unfavourable benefit-risk balance.

KEYWORDS: Vaccine, COVID-19, pandemic, pharmacovigilance, adverse drug reaction.

1. Introduction

The COVID-19 pandemic affected nearly every aspect of life, from global health systems to technology and communication networks, reshaping work, education, and social interactions on an unprecedented scale. It had a profound impact on healthcare delivery, with disruptions to routine care [1-3] as well as on mental health and child development [4-6]. Educational systems underwent massive transformations with the widespread adoption of remote learning, altering teaching methods [7,8]. The COVID-19 pandemic posed significant challenges also to regulatory institutions and the pharmaceutical industry. Pharmacovigilance (PV) operations underwent significant changes, including widespread adoption of remote work, accelerated automation initiatives, and redesigned workflows to manage rising case volumes driven by new COVID-19 treatments and vaccines [9-11].

COVID-19 vaccines developed and released since 2020 underwent the standard rigorous testing and evaluation before being approved for use. However, as with any medication, it was important to continue monitoring their safety and effectiveness through postmarketing surveillance to detect rare or unexpected adverse events (AEs) that may not have been identified in the clinical trial setting. Due to mass vaccination campaigns, there was an unprecedented volume of safety data from spontaneous reporting systems, the scientific literature, and pharmacoepidemiologic studies. To ensure enhanced monitoring of emerging vaccine safety information, the European Medicines Agency (EMA) issued an ad hoc guidance recommending intensive monitoring of reports of AEs of special interest and the use of observed-to-expected (O/E) analyses [12].

Consequently, manufacturers rapidly adapted and expanded existing PV systems, such as increasing case-processing capacity, while ensuring all changes remained fully compliant with regulatory obligations. The industry perspective in managing unprecedented amounts of safety data to meet regulatory requirements during the COVID-19 pandemic is presented in this paper based on Pfizer-BioNTech Comirnaty vaccine data.

An outline of the academic perspective, including scientific associations, is also provided concerning its role in voicing scientific opinions and creating standards that both health authorities (HAs) and the pharmaceutical industry needed to consider.

2. Regulatory perspective

The rapid development and worldwide rollout of the COVID-19 vaccines, which happened at the end of 2020, was a turning point not only in the COVID-19 pandemic but also in the PV system. This period compelled the existing PV infrastructure to adapt rapidly to process a large volume of safety reports while remaining fully compliant with regulatory requirements, despite widespread challenges such as staff shortages. The vaccines were impatiently expected by governments, healthcare systems, and patients worldwide [13,14]. The first authorized vaccine under conditional approval was the Pfizer/BioNTech Covid-19 vaccine – Comirnaty – at the end of 2020.

Conditional approval is used for medicines that are intended to be used for serious or life-threatening conditions when early clinical data indicate a positive risk-benefit profile and the product fulfils the unmet medical need [15]. In this special circumstance, the available clinical evidence must show that the expected benefits of immediate availability of the product outweigh the risks. The manufacturer is required to provide complete data post-approval. Standard approval is used when there is no urgent public health need and is granted only when complete evidence on safety and efficacy required in the standard approval process is available [15].

By 2022, Comirnaty received standard marketing authorization and was also granted an indication for use in adolescents and children. One of the main challenges for the governments, healthcare providers, and HAs was how to effectively conduct population-based vaccination programs on a large scale. The EMA's COVID-19 vaccine safety update of 8 December 2022 reports that Comirnaty and Spikevax were the most commonly administered vaccines in the European Union and European Economic Area (EU/EEA) region (Appendix, Fig. A1). About 685 million doses of Comirnaty vaccine, including about 57.3 million doses in children and adolescents (younger than 18 years), and about 161 million doses of Spikevax vaccine, including about 3.1 million doses in children and adolescents (younger than 18 years), were administered in the EU/EEA since the authorization until 13 November 2022 [16].

Drug safety profile monitoring requires detecting safety signals, i.e., information arising from one or multiple sources, suggesting a new potentially causal association or a new aspect of a known association. Signals can be detected via different sources, most notably via spontaneous reporting of AEs. Therefore, the collection of AEs associated with the use of the vaccine and its real-time analysis for signal detection purposes became an urgent priority to continuously validate the vaccine risk-benefit profile.

Local HAs, as the main contact for patients and HCPs in national PV systems, from the very beginning of the vaccination programs, were overwhelmed with thousands of COVID vaccine-related individual case safety reports (ICSRs), which contained information on suspected adverse drug reactions (ADRs) related to individual patients. In line with the standard safety data management process in the EEA, local HAs share ICSRs throughout the EudraVigilance database (a system for managing and analyzing information on suspected ADRs operated by EMA) with appropriate stakeholders, including other agencies, marketing authorization holders (MAHs), and, in a cumulative view, with public users [17].

A significant diversification in the number of cases reported to the EudraVigilance database could be observed among different countries. As shown in Appendix, Fig. A2, the highest numbers of reported cases within the EEA region were recorded for Germany, France, the Netherlands, Austria, and Italy. Due to an unprecedented number of safety reports received, local HAs were forced to develop some innovative and automated solutions to enable near real-time safety profile assessment. Chosen relevant examples are provided in Table 1.

In parallel, there was a need to quickly develop new PV requirements and regulations to address safety needs during the pandemic and to satisfy the public interest of vaccines safety profiles. This required additional effort and an intense workload from regulators. To reduce implementation time, the new PV requirements were often introduced by posting new guidance on the HA website, providing it directly via email to MAHs or communicating during virtual meetings with industry stakeholders. COVID-19 pandemic experience stimulated countries that did not have PV requirements before e.g., Bahrain, Quatar, to introduce specific guidance for collecting AEs specifically for the COVID-19 vaccine.

In certain situations, effective dialogue between HAs and MAHs helped fulfil new obligations, benefiting the local community and enabling the prompt identification of potential novel risks (signals) at the specific population level. One interesting justification for the introduction of some of those special requirements was the desire to obtain information as soon as possible, before the reporting party (e.g., patient) shares it in social or public media. While the value of social media as a source of information on ADRs is not disputed, its nature may cause unnecessary information chaos or produce fake news without prior medical verification.

It is noteworthy that these extraordinary approaches and requirements created a significant additional workload for regulatory authorities. Accelerated reporting timelines and additional specific requirements that were introduced by EMA [12]meant that data had to be processed, analysed, and acted upon far more rapidly, creating significant operational and analytical challenges.

Table 1. Regulatory strategies to enable near real-time safety profile assessment.

Regulatory Authority	Solutions
EMA	ACCESS initiative International collaboration on observational research through the ICMRA [68,69]
CBER at the FDA	Passive and active safety surveillance systems: - Collaboration with the CDC, CMS, Department of Veterans Affairs, other academic and large nongovernment healthcare data systems; international collaboration. - Use of BEST system, EHR, and linked claims-EHR databases [70]
Lareb,Netherlands Health Authority Agency	Development of an automatic processing of well-known AEFIs reported during a large-scale vaccination campaign. A COVID-19-tailored vaccine web-based reporting form. A fully automated process for ICSRs enabled the handling of the majority of common and known reported AEFIs. Signal detection meetings and weekly reports for batch analysis, resulting in 99.9% of the ICSRs being processed within the compliance timeframe to EudraVigilance [71].
ANSM, French Health Authority Agency	Enhanced PV system, carried out by 31 regional PV centers in France, including routine PV and specific weekly, bimonthly, or quarterly reports for the vaccines, heterologous regimen, and vaccination during pregnancy. Increased efficiency in identifying signals [72].
AIFA, Italian Health Authority Agency	The PV system based on the national centers developed before the pandemic was appropriate for the unexpected increase of case volume, and no backlog was observed at the AIFA level. On 22 June 2022, a new National Pharmacovigilance Network was launched [73].
NoMA, Norwegian Health Authority	NOMA focused on management of a large volume of cases and also on providing transparently near real-time evaluation effects, publishing weekly reports for AEs during the pandemic, and also communicating in good time potential issues [74].
Polish Health Authority	Electronic reporting of AEFI has been made compulsory for HCPs. Compensation fund created for people experiencing vaccine ADRs [75,76].
Israel Health Authority	An online platform for AEFI reporting made available to the public [78]. A designated team of experts appointed to analyze data [77,78]. Regular communication to the public by the Ministry of Health [79].

ADR, adverse drug reactions; AE, adverse event; AEFI, Adverse Events Following Immunization; AIFA, Agenzia Italiana Del Farmaco; ANSM, Agence nationale de sécurité du médicament et des produits de santé; EMA, European Medicines Agency; ACCESS, vACcine Covid-19 monitoring readinESS; BEST, Biologics Effectiveness and Safety; CBER, US Center for Biologics Evaluation and Research; CDC, Centers for Disease Control and Prevention; CMS, Center for Medicare and Medicaid Services; EHR, electronic health records; FDA, US Food and Drug Administration; HCP, healthcare professionals; ICMRA, International Coalition of Medicines Regulatory Authorities; NOMA, Norwegian Medicines Agency.

3. Industry perspective

Some studies showed how pharmaceutical companies of different sizes were impacted by the COVID-19 pandemic in terms of PV activities and how these companies responded to the challenges of a changing landscape in terms of PV infrastructure and practices [11,18]. For Pfizer, a key challenge in post-marketing surveillance of the COVID-19 vaccine was the rapid global distribution of large numbers of doses alongside simultaneous mass immunization programs, which led to an unprecedented volume of reported ICSRs (Fig. 1).

The ICSRs submission requirements were challenging, not only due to high volumes of expedited reports but also due to extraordinary novel requirements that many regulators worldwide had introduced upon the vaccine authorization for specific types of ICSRs e.g., Monthly Summary Safety Reports (MSSR), ad hoc requests, and enhanced signal monitoring [19]. Additionally, new safety aggregate reports were requested by competent authorities, such as

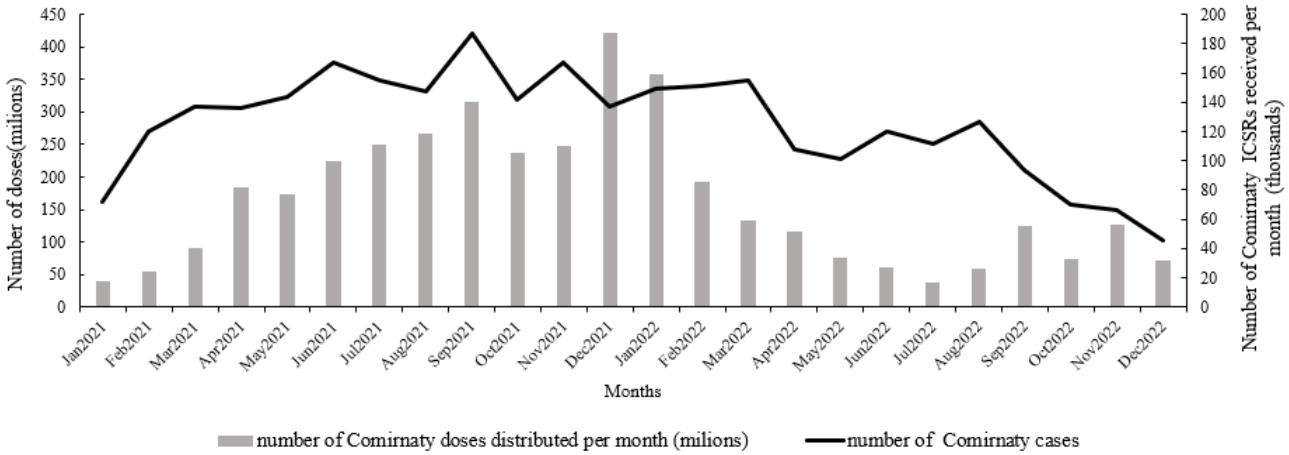

Fig. 1. Pfizer global monthly Comirnaty ICSR volume received against Comirnaty doses distributed: ICSR, individual case safety report. (Pfizer internal data. Presented with permission for the purposes of this publication.)

the Summary Monthly Safety Report (SMSR) prepared every month, in addition to standard Periodic Safety Update Reports (PSURs) and ad hoc EMA Pharmacovigilance Risk Assessment Committee (PRAC) requests.

The widespread media coverage of the vaccines and the importance of their personal safety raised awareness and encouraged more people to report any ADRs. Moreover, the use of online electronic forms made it easier for individuals to report. This may have also contributed to an increase in already stimulated reporting. All AE reports needed to be thoroughly reviewed and investigated by PV systems to ensure the ongoing supervision of the safety profile of the vaccines and to capture potential new signals.

It became evident for Pfizer within the first few weeks after the Comirnaty launch in the United States, United Kingdom, and EU that ICSR intake for the vaccine was ten times higher than expected based on influenza vaccines experience [20]. Fig. 1 shows how the number of Comirnaty ICSRs evolved versus the number of doses distributed during the first months after authorization, resulting in a tremendous increase in the workload. At the same time, the rate of serious cases was much higher than initially predicted and required focus [19-21]. To overcome the identified challenges, Pfizer reacted promptly, adapting to the change and implementing new resources, technologies, and processes to efficiently manage the influx of AE reports. The aim was to ensure maintenance of efficient PV system operation for the vaccine and all other products Pfizer continued to deliver to patients. The evolution of Pfizer resources is outlined in Fig. 2. A summary of operational changes implemented by Pfizer is presented in Table 2.

Table 2. Evolution of resourcing model and operational changes applied in Pfizer.

Change implemented	Description
Deprioritized ICSRs	Deprioritized strategy required additional robust quality operations to ensure no serious cases were left among deprioritized cases. Strategy decisions were transparently communicated with regulatory authorities during regular meetings.
Increase the number of PV specialists	Extensive employment of temporary employees and vendors (Fig. 2).
Improved use of platforms	Pfizer already had an in-house solution for workload peaks that was started before the pandemic. The regional platforms created to support different PV teams in multiple countries allowed for well-trained resources localized in different time zones since the beginning of the increases in COVID-19 vaccine ICSRs.
Vendors	The COVID-19 steering committee was established, allowing for prediction-based planning to estimate the number of employees required and to assess hiring additional vendor resources (Fig. 2). Additional training and supervision were implemented to ensure that the vendors were working in accordance with established standards and procedures.
Automation in receiving ICSRs	Pfizer implemented automated activities for triage of the intake and also E2B acceptance of EV-WEB and MHRA reports, saving time without compromising quality. Automation at this workflow stage was crucial to enable correct prioritization. Additionally, having all the reports minimally logged into the database upon receipt enabled regular scanning of the pending reports to identify any that needed to be prioritized.
RPA	RPA was also implemented to automate the initial data entry of reports, which significantly sped up case processing. By using natural language processing and machine learning algorithms, the bots were able to extract information quickly and accurately from reports and enter it into the relevant fields in a database. RPA was programmed to perform basic validation checks on the data, further increasing the efficiency of the case processing workflow. This allowed staff to handle a larger volume of cases and to focus on more meaningful work.

E2B – eng. Electronic to Binary, the international standard for electronically transmitting individual case safety reports; EV-WEB, EudraVigilance Web reporting tool; ICSR, individual case safety report; MHRA, Medicines and Healthcare product Regulatory Agency; PV, pharmacovigilance; RPA, robotic process automation.

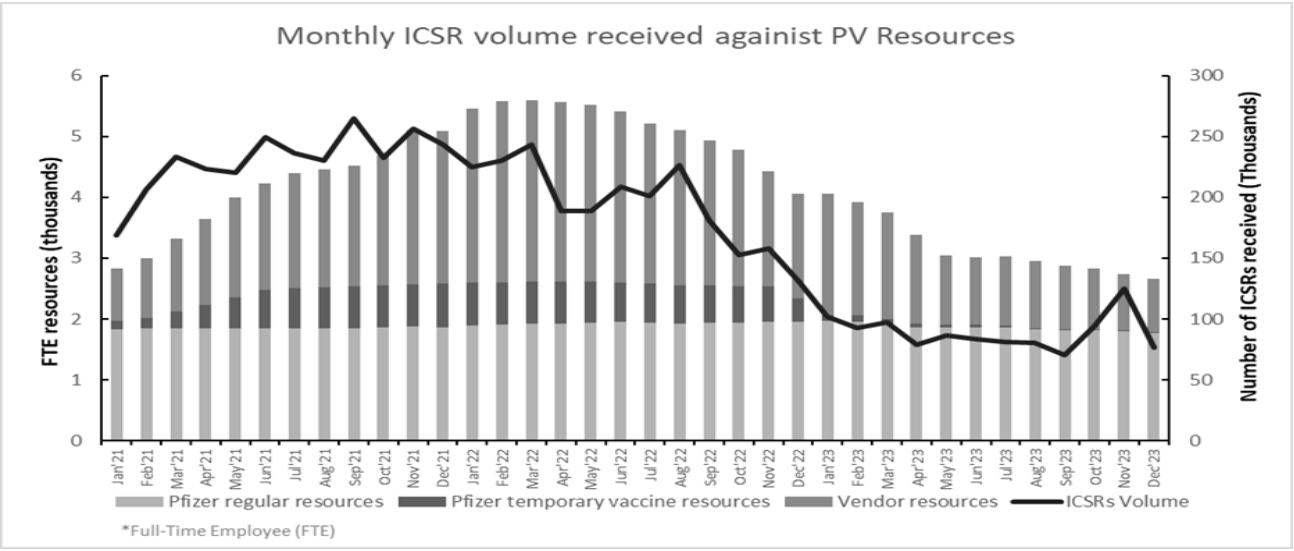

Fig. 2. Pfizer monthly total ICSR volume received against PV Resources in 2021-2023: FTE, full-time equivalent; ICSR, individual case safety report; PV, pharmacovigilance. (Pfizer internal data. Presented with permission for the purposes of this publication.)

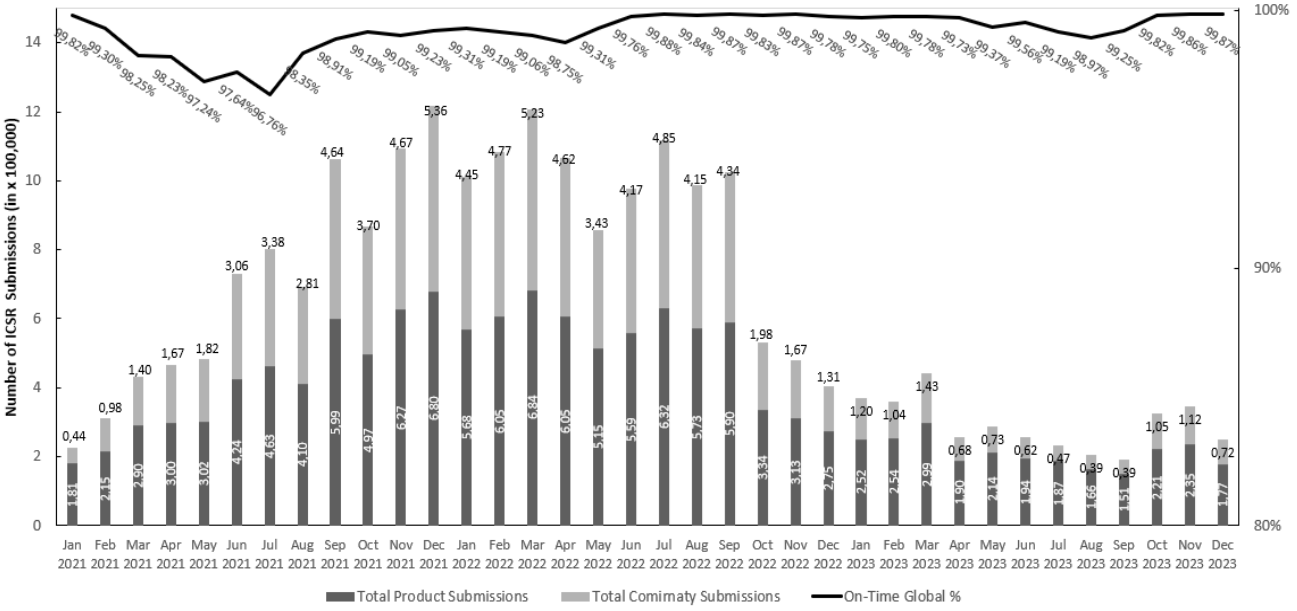

Fig. 3. Pfizer global regulatory submission compliance in 2021-2023: ICSR, individual case safety report. (Pfizer internal data. Presented with permission for the purposes of this publication.)

Another fundamental risk to the efficiency of the PV system, faced by both the pharmaceutical industry and HAs, was a reduced workforce resulting from employees contracting COVID-19. A smaller staff still needed to work under the same tight timeframe while maintaining attention and quality in all processes. This led to increased stress and difficulties in maintaining productivity. Many companies faced a major challenge in adapting to potential staff losses and ensuring operations could continue with fewer resources. Additionally, the necessity to work remotely and other measures to maintain social distancing also added to the strain on the workload. Based on the authors' professional experience within the pharmaceutical industry, often, employees had to work longer hours or take on additional responsibilities. All these challenges required excellent people management and measures to reduce burnout risk.

As presented in Fig. 3, despite an unprecedented increase in safety data, Pfizer fulfilled regulatory obligations globally, submitting ICSRs with very high compliance with established timelines for the whole pandemic period, proving the flexibility of the already existing PV model, and that the decisions made and actions taken based on the changing situation worldwide were accurate.

4. Academia perspective

4.1. Increased workload in research and evidence appraisal

The work of researchers undertaken to understand and control the disease resulted in large numbers of scientific publications, including those addressing COVID-19 treatment options, as well as the efficacy and safety of COVID-19 vaccines. The amount of research carried out worldwide meant that researchers and HCPs were faced with an unprecedented amount of published information that needed to be analysed and translated into clinical practice [22]. Most COVID-19–related publications were easily accessible to the scientific community as arrangements were made by publishers to make them available in open-access repositories. HCPs were struggling to find guidelines, while the time pressure and the uncertainty of the development of the pandemic were adding to the chaotic situation. Several centres were trying to summarise the information regarding possible treatment options and translate the results into manageable pieces of information. An example of these efforts was the American Society of Hospital Pharmacists database where the evolving evidence for available treatment options was summarised in a convenient form [23]. Similar actions were undertaken by many other organizations, such as the National Institute for Care and Health Excellence (NICE) [24] or The Public Health Agency of Canada, together with the COVID-19 Evidence Network to support Decision-making (COVID-END) [25]. In Poland, the Agency for Health Technology Assessment and Tariff System created a scientific publication radar – an open-access tool gathering evidence in the field of COVID-19 pharmacotherapy (including prophylaxis). In December 2022, the number of all scientific reports listed in the tool reached nearly 162,000 [26]. These summary reports required the integration of current safety data to provide balanced benefit-risk assessments. Specifically, the evidence synthesis involved a systematic review of AE reports and safety outcomes reported in the literature [25,27].

Alongside the publication radar, between December 2020 and March 2022, the agency conducted regular reviews of international guidelines for COVID-19. The search strategy involved checking the contents of several websites of government and non-government organizations, including the World Health Organization (WHO), the European Centre for Disease Prevention and Control, the National Institutes of Health, and the Chinese Centre for Disease Control and Prevention. The last available review was published on 18 March 2022, but the archives contain more than 60 documents detailing updates of international recommendations and strategies for managing the disease [27]. The agency was also responsible for preparing rapid reviews for emerging treatment options and continuously updating summaries

of evidence on COVID-19 pharmacotherapy [28]. The updates needed to be frequent because new data were becoming available at a fast pace. On a global level, the WHO created a COVID-19 research database gathering articles published worldwide. As of February 2023, the database contained more than 800,000 entries in total, approximately 10% of them relating to COVID-19 vaccinations [29].

Early in the COVID-19 pandemic, several publications generated misleading hypotheses — such as those supporting hydroxychloroquine and azithromycin use [30], which led to widespread confusion and impacted clinical decisions negatively [31]. Although the misleading nature of some claims is clear in retrospect, it was not obvious at the onset of the pandemic. The overestimation of potential benefits was driven by the urgent need to identify effective treatment. These claims were later fully evaluated, but time was needed to reach conclusions.

Providing reliable information to support HCPs in making clinical decisions remained a major concern for the academic community. Various teams of experts were reviewing the most up-to-date evidence on COVID-19 to help translate it into guidance and recommendations, as well as to facilitate the development of educational resources. Universities were involved in providing guidance relating, not only directly to COVID-19 prevention and treatment, but also to managing patients' care in extreme circumstances of the pandemic. An example of these efforts is a guide for medication management developed by a team of experts at the University of Maryland School of Pharmacy with assistance from the US Deprescribing Research Network, offering practical advice on how to optimise pharmacotherapy in post-acute and long-term care settings [32].

4.2. Vaccine-related workload

4.2.1. New vaccine technology and rapid vaccine rollout

The accelerated process of introducing the COVID-19 vaccine, combined with the start of vaccination programs in vulnerable populations, such as the elderly or patients with a higher risk of unfavourable COVID-19 course, enforced significant engagement of members of the academic community in shared decision-making. There was a great need for gathering and summarising information regarding ADRs following COVID-19 vaccinations. This would have been the case with any new medicine, but in the case of vaccines against the pandemic strain, the worldwide vaccination campaign, as well as the variety of populations receiving the vaccine, meant the amount of data to analyse and the level of safety concern was enormous. It should also be stressed that many new challenges emerged from introducing relatively new mRNA technology in COVID-19 vaccine development. Experts at the London School of Hygiene and Tropical Medicine (London, UK) developed an online vaccine tracker (launched in April 2020) [33]. The tool was designed to collect up-to-date information on all COVID-19 vaccines in development, present them in a user-friendly way, and keep the public and HCPs informed of the fast-paced developments. Limitations that normally exist for newly marketed medicines multiplied enormously in the case of COVID-19 vaccines due to the urgent need to vaccinate as many people as possible in the shortest period. This meant that safety information, including detection and management of AEs following immunization, had to be collected and analysed effectively to consider the effects in special populations [34].

4.2.2. Adverse events and vaccine safety, including special populations

The role of academia involved informing about ADRs and offering a scientific explanation of the possible mechanisms and risk factors, disseminating knowledge about populations at risk, and suggesting scientifically justified management. The academic community, through critical analysis, put published data in perspective and worked on interpretations that could be translated into clinical practice. The publications stressed the importance of being cautious in interpretations and carefully exploring the limitations of each study. Reviews and analyses of published evidence served as the basis for ways of development and further research that could be considered by both the industry and academia.

Experts in different scientific fields were trying to determine the molecular mechanisms of COVID-19 vaccines' adverse effects. A quick review of popular scientific databases showed widespread collaboration, including, to enumerate only a few, molecular biology, biochemistry, and tropical medicine [35]. One of the first major concerns that attracted public attention was the risk of thromboembolism associated with COVID-19 vaccines. Shortly after the COVID-19 pandemic started, it became known that SARS-CoV-2 infection was associated with the risk of developing thrombosis. Pulmonary macrothrombi and microthrombi were identified in autopsies of patients with COVID-19 [36-38]. Soon after, reports of venous thromboembolism (VTE) after vaccination appeared, which led some European countries and the United States to temporarily pause the administration of vaccines. Increased efforts were made to explain the phenomenon [39].

The Brighton Collaboration Thrombosis and Thromboembolism Working Group, consisting of several clinical, public health and PV experts, since September 2020 regularly reviewed results from literature searches and worked on the development of case definition and guidelines for data collection, analysis and presentation of AEs occurring after immunization [40]. In their statement, the authors reviewed the 143 positions of literature and defined a system of classification of cases taking into account diagnostic certainty for venous and arterial thromboembolism.

Another serious concern was the occurrence of acute ischaemic stroke following COVID-19 vaccination. The relationship was initially undefined, and systematic reviews of case reports and their series allowed for obtaining a clearer picture. One of the examples of a systematic review is the publication of Rahmig et al. [41]. The authors reviewed 208 articles and concluded that the risk of acute ischaemic stroke did not appear to be increased in patients who received approved SARS-COV-2 vaccines at that time. The authors stressed, however, that the follow-up in the review was limited to 6 months after vaccinations. Another limitation was the observational nature of the studies included [41].

The efforts of academia to summarise information regarding AEs following vaccinations were extensive and beyond the standard approach, to give as

an extraordinary example, the elaboration of a checklist to improve the quality of autopsies being conducted following death due to COVID-19 vaccinations [42].

It was also essential to assess the efficacy and safety of vaccines in special cohorts initially excluded from the pivotal trials, such as pregnant and breastfeeding women, children, or immunocompromised patients. This meant more data to be collected, analysed, and translated into clinical practice in a short time [43-46]. Scientists and physicians all over the world gathered and published data on using the anti-SARS-CoV-2 vaccine in various special populations. Examples include patients with autoimmune diseases, such as multiple sclerosis [47,48], rheumatic diseases [49], cancer [50,51], and other immunocompromised patients [52-55]. On this basis, scientific associations and societies were analysing data and soon issuing recommendations about vaccinations for patients with specific diseases and later advice for booster doses. These were international and national guidelines. One example of these efforts could be the American Academy of Neurology Covid-19 resource center, designed to keep neurology professionals and patients informed on recent developments [56].

The rapid development and deployment of COVID-19 vaccines during the pandemic led to an unprecedented volume of publications; however, many of these were of low quality due to the urgency to disseminate findings quickly. This haste often resulted in overinterpretation of data, potentially misleading both the scientific community and the public [57]. Meanwhile, pharmacovigilance databases like EudraVigilance provided large real-world datasets for continuous safety monitoring [58], helping researchers validate findings, assess risks, and guide public health decisions.

4.3. Addressing vaccine hesitancy

Addressing vaccine hesitancy is a unique activity in academia, a field that escapes HA and the pharmaceutical industry. A broader view that goes beyond a strictly medical approach was essential to address th is issue. The need to manage the safety concerns of patients and HCPs became clear even before the COVID-19 vaccines were made widely available. Early reports on post-vaccination AEs, including VTE risk, among many other factors, might have exacerbated vaccine hesitancy. It needs to be stressed that even people not opposing vaccinations were apprehensive about the COVID-19 vaccines because of the unusually fast pace of their development and because many were becoming aware of mRNA vaccine technology for the first time. In February 2023, over 3500 articles on COVID-19 vaccination hesitancy were listed in PubMed [59].

The whole scientific world was eager to get to know the factors responsible for this phenomenon. It could be easily seen that much effort was made in different parts of the world to determine and improve the situation. A study conducted in Canada before the COVID-19 vaccine was widely available and in the earlier stages of the vaccine rollout showed that the novelty of the mRNA technology, rapid approval of the vaccine, and lack of long-term safety data were the reasons why people were hesitant to receive the vaccine. Interestingly, some study participants remained hesitant even after getting a COVID-19 vaccine dose [60]. A study conducted in Poland in the autumn of 2021 among patients with inflammatory bowel disease showed that 50% (n=38) of patients who did not receive the vaccine were concerned about ADRs, and one-third of patients were worried the vaccine could cause exacerbation of their disease [61].

The role of regulators and HA, which centered on vaccine approval, safety monitoring, as well as vaccination campaign logistics, was complemented by academic institutions through research-driven education and targeted efforts to counter misinformation. Public statements were made by members of academia to address the misinformation and lack of trust towards vaccinations. Stanford Medicine held a virtual conference inviting experts to discuss how to tackle vaccine hesitancy and tackle false and misleading claims around COVID-19 vaccination [62]. The Inter Academy Partnership (IAP), an organisation uniting more than 140 national, regional and global member academies of science, medicine and engineering, produced several resources aimed at countering the COVID-19 vaccine hesitancy, including holding a Global Webinar on Countering Vaccine Hesitancy (which took place 23 March 2021), followed by a report to help academies prepare for national vaccination efforts [63]. To support 2021 World Immunization Week, IAP released several videos and an infographic on the different types of COVID-19 vaccines, their development, and mode of action [64].

5. Long-term safety monitoring of COVID-19 vaccines

Since the initial introduction of COVID-19 vaccines over four years ago, extensive ongoing safety monitoring has confirmed that their safety profile remains consistent with early findings [58,65]. Large-scale surveillance data indicate a stable frequency of ADRs reported over time, with no significant changes in rates of common reactions reported [58,66]. AESI continue to be monitored and analysed [67]. Understandably, continued safety monitoring is still needed.

6. Conclusions

The COVID-19 pandemic, leading to exposure of hundreds of millions of people worldwide to COVID-19 vaccines, triggered an unprecedented volume of work for HA and the pharmaceutical industry. The academic community faced the urgent task of explaining scientific knowledge about the vaccines' safety profile to the public and addressing vaccine hesitancy.

The pandemic highlighted the key role of planning, especially for functions managing case volumes, human resources, and real-time decision-making. For both the HA and the pharmaceutical industry, technology efficiency, especially utilizing advantages in case processing automation and eliminating manual effort (often associated with bottle necks), appeared to be essential to sustain the PV system. It is also important to highlight the role of real-time communication and transparency about vaccine benefits and risks among all stakeholders, including HCPs, patients, payers, and the public, not just regulators and industry.

The industry stakeholder was able to react quickly and effectively, which led to a continuous improvement in processes and procedures in COVID-19 vaccine safety monitoring. It provided real-world data for authorities and university representatives to draw reliable safety information. The changes implemented have been used to guide and shape the future of PV.

The COVID-19 pandemic provided an unprecedented opportunity to test the resilience of the global framework of evidence assessment and decision-making. The rapid spread of the virus, combined with the urgent need for timely decisions, exposed significant challenges in how information is generated, disseminated, and translated into clinical practice. This experience highlights the critical need for robust mechanisms to prevent harm during future health crises and ensure evidence-based clinical practice.

All the stakeholders mentioned in this article gained insights through COVID-19 pandemic experiences, which, although sometimes applied differently, were relevant to each of them. These experiences have given us new skills and tools for managing future PV workloads. It is a unique and universal experience from which we can learn and benefit in similar critical situations in the future.

Appendix

Pharmacovigilance challenges of COVID-19 vaccine safety monitoring during the pandemic

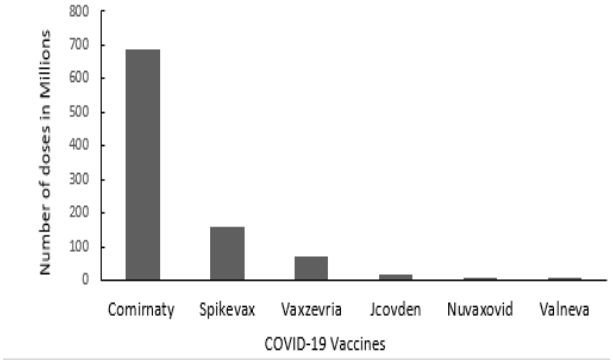

Fig. A1. Number of doses reported (in millions) administered to patients of all age groups for different COVID-19 vaccines from authorization date until 13 November 2022 for EU/EEA region. These data were obtained from the EMA COVID-19 Vaccines Safety update report published on 08 December 2022. EEA includes Iceland, Liechtenstein, and Norway. EMA, European Medicines Agency; EEA, European Economic Area.

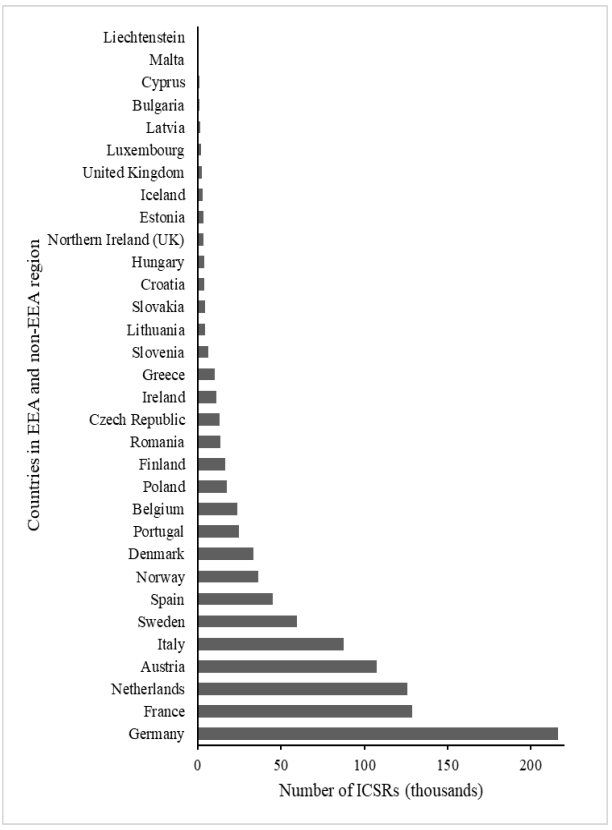

Fig. A2. Number of ICSRs for Comirnaty Monovalent (Tozimeran) in EEA and non-EEA countries existing in the EudraVigilance database as of 08 May 2023. ICSR, individual case safety report; EEA, European Economic Area.

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