

Technical meeting report

Unmasking safety signals during a pandemic
Virtual meeting – 6 December 2021

Executive summary

The World Health Organization (WHO) Pharmacovigilance team organised a webinar on 6 December 2021 to bring together worldwide experts to discuss how the current pharmacovigilance systems and approaches used are performing and how to ensure they can deliver in a pandemic. The current COVID-19 pandemic has put pressure on pharmacovigilance systems due to many reasons, including the rush to repurpose existing treatments, with the appearance of substandard and illicit products in response to high demands. Consequently, healthcare professionals are reluctant to report ADRs related to these products. In addition, the rapid roll out of vaccines has given rise to the need to communicate about extremely rare AEFIs associated with lifesaving vaccines. Many patients, especially those with chronic conditions, face difficulties to access health care, including regular monitoring, hospital appointments and surgical interventions resulting in increasing all-cause morbidity and mortality rates.

WHO has provided support for surveillance of adverse events following immunization (AEFIs) in countries over the last two decades in many low-to-middle-income countries (LMICs). This investment has meant that most have been able to adapt their existing AEFI surveillance systems to support COVID-19 vaccine safety surveillance rather than develop whole new systems. Since the rollout of COVID-19 vaccination programmes, there has been a sharp rise in AEFI reporting which has inundated immunization programmes and regulators with work to evaluate and respond to these reports and to undertake the complex risk-benefit communication that follows. Health budgets are being stretched as countries need to buy COVID-19 vaccines, invest in additional pharmacovigilance activities and risk communications, as well as treat patients with severe COVID-19.

Infodemics occur when large amounts of information are generated, both valid information as well as misinformation. The huge mass of COVID-19 information is spread via digital and physical information systems making it difficult to find trustworthy information sources when reliable information is most needed. Infodemic management requires a good understanding of the concerns and questions in different communities to guide the communication strategy and the rollout of the vaccination programme.

WHO has invested in technology for digital real-time on-line listening, the Peek Platform which is an early warning system for COVID-19 vaccine-related events. This platform uses artificial intelligence (AI) to identify information on COVID-19 vaccine-related events on Internet and public social media platforms and news outlets in English, Spanish and Russian. In November 2021 over 175 000 documents were identified daily, with about one-third being Internet articles. This system has been shown to detect safety signals which can then be investigated more rapidly than with the traditional reporting mechanisms and thus enable timely communication to avoid the circulation of misinformation.

Individual case safety reports (ICSRs) are the more traditional source for the identification of safety signals. The timely processing and assessment of the large number of ICSRs received since the rollout of COVID-19 vaccines and medicinal products for prophylactic and curative treatment of COVID-19 is a challenge. Machine learning (ML) and natural language processing (NLP) are two AI technologies that are being investigated for processing and assessing ICSRs using algorithms. However, these technologies are not a substitute for human expertise. The challenges for the routine use of these technologies include ensuring the algorithms are specific across different systems and addressing confidentiality issues related to personal information in narratives that are processed.

The number of ICSRs received by Uppsala Monitoring Centre (UMC) after the implementation of COVID-19 vaccine programmes is equivalent to the total number received in its first 40 years of operation. In the UK almost 400 000 spontaneous reports, with almost 1.3 million events, have been received up to 24 November 2021. Various disproportionality analytic approaches are used to assess if the number of reports for adverse events of special interest (AESIs) is higher than expected but each approach has limitations. Hence, new statistical methods are needed for the current large volume of ICSRs, that should be combined with clinical expertise and wisdom to evaluate signals and take decisions. Electronic health records and other databases need to be harnessed to provide complementary data not available in the ICSRs. Better collaboration between those analysing spontaneous reports and those doing epidemiological studies could facilitate this.

The main objective of public health and pharmacovigilance systems is the protection of populations. The prioritization of signal processing should include rapid exploration of any signal that is medically and pharmacologically plausible if it is likely to have a significant impact on the population. In the past pharmacovigilance systems identified rare, specific events, with a strong association with treatment exposure (relative risk >5) and a short delay to onset, but these events generally have a low public health impact. The current challenge is to assess more common diseases, with a longer delay to onset and a weaker association with treatment exposure (relative risk <2) because these may have a greater public health impact. Access to larger global databases will help overcome this challenge.

Pandemic preparedness has been key for the successful management of expected AEFIs. For example, the core requirements for COVID-19 vaccine risk management plans (RMPs) were developed to facilitate and harmonise their preparation and evaluation. However, pharmacovigilance systems face new real challenges for signal detection of unexpected events at national and international levels. For COVID-19 vaccines, there is a recognized need for observational post-authorization safety studies (PASSs) to assess identified and potential risks. The ACCESS project ('vACCine Covid-19 monitoring readinESS') has identified a European network of data sources that could be used to investigate specific research questions on COVID-19 vaccines and epidemiological methods to monitor the safety, effectiveness and coverage of COVID-19 vaccines. One of its most important achievements was developing the mechanisms for estimating background rates of adverse events of special interest (AESIs) and other relevant conditions which are essential to those conducting observed vs expected analyses in the assessment of ICSRs for specific AESIs.

The current pandemic situation could be leveraged to improve pharmacovigilance systems by encouraging two-way collaboration between LMICs and high-income countries. WHO and UMC have set up effective collaboration with their global safety database, on-line data entry systems, as well as training to build capacity in LMICs. Training, targeted communication and active encouragement to report safety events, particularly in LMICs could improve pharmacovigilance systems.

We are in an unprecedented situation where medicinal products (vaccines) have been rapidly developed to be used in the whole population, i.e., 7 billion humans. Although traditional pharmacovigilance systems were not designed for this workload, they have provided a basic response to healthcare systems but they need to be improved. The COVID-19 pandemic is an opportunity to improve them and to adopt new technologies described above. WHO is looking to start consultation in new technologies and methodologies for pharmacovigilance with the Member States and to initiate a public consultation process to allow the whole community to voice their opinions. During

this workshop, three potential actions to move forward were identified. Firstly, set up a working group to look at the limits of the disproportionately approach, identify additional data sources for pharmacovigilance and different methods adapted to specific settings. Secondly, set up another working group to look at the impact of signals, particularly in LMICs, and how they can be helped by providing support for processing the signals, taking into consideration their situation and their available resources. Thirdly, a mapping exercise of all regional, national, and international, public, and private initiatives should be undertaken to avoid reinventing the wheel.

Introduction

In the context of the current COVID-19 pandemic, new medicinal products, particularly vaccines, have become widely available in an unprecedented record time. This has meant that the expectations from pharmacovigilance systems have been, and continue to be, tremendous. It is more critical than ever that countries have efficient pharmacovigilance systems that will enable them to monitor and pick up new safety signals associated with these products and to address and manage any emerging risks in an efficient, timely manner.

The WHO Pharmacovigilance team organised a webinar on 6 December 2021 to bring together worldwide experts to discuss how the current pharmacovigilance systems and current approaches used are performing and what can be done to ensure these can deliver in a pandemic.

Challenges and opportunities for pharmacovigilance during pandemics

The COVID-19 pandemic has raised many challenges. For example, there was a scramble to repurpose existing treatments, including untested therapies such as hydroxychloroquine, and ivermectin. The high demand for these treatments encouraged the appearance of substandard and illicit products and clinicians using these products are often reluctant to report adverse drug reactions (ADRs). Also there have been concerns raised about drug-disease interactions, such as the safety of ibuprofen and angiotensin-converting enzyme (ACE) inhibitors in patients with COVID-19 disease. Regulatory authorities and ethics committees face the challenges of ensuring quick turnaround times for reviewing clinical trial applications, product submissions for licensing, new signals and changes in treatment policies as new evidence emerges, all emphasizing the need for robust pharmacovigilance systems. Public health officials and regulatory agencies have been inundated with requests to provide input on complex issues around epidemiology, trial design and causality. Communicating extremely rare risks of harm associated with lifesaving vaccines, with sensitivity to the local context, in an environment that is charged with expectation and fear requires sophisticated communication skills which are not always readily available. Finally, in the background, all-cause morbidity and mortality rates are rising with patients not able to attend hospital appointments, undergo surgery, get their chronic medication or have their biochemical parameters, such as warfarin or valproate levels, checked.

While the webinar focused on vaccines, since the pandemic was declared in March 2019 many public health measures and therapeutic interventions have also been introduced (Figure 1).

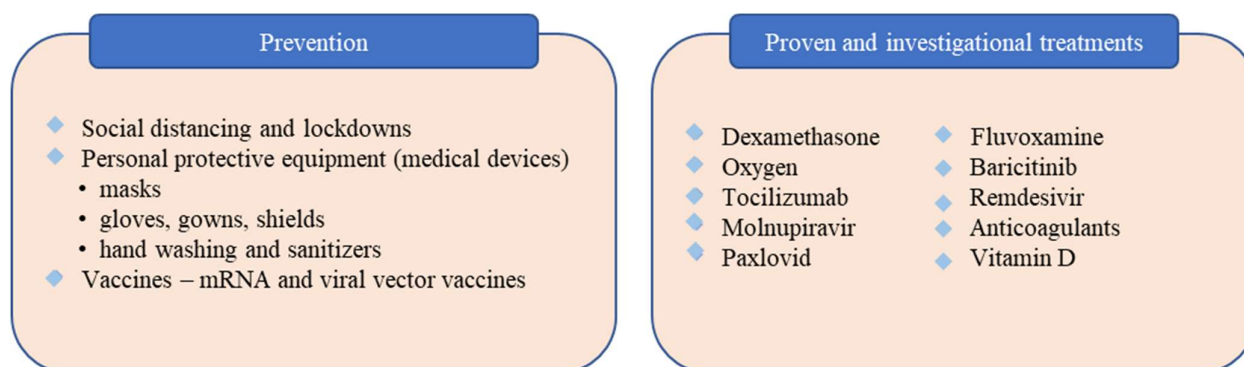


Figure 1: Public health measures and therapeutic interventions introduced since the start of the COVID-19 pandemic

Pandemic pharmacovigilance needs to incorporate all therapeutic interventions including medical devices. Regional coordination and collaboration have become critical to optimize limited resources and avoid duplication. The work done over the last two decades by WHO to support adverse event following immunization (AEFI) surveillance in countries, has meant that most have been able to adapt their existing AEFI surveillance systems to support COVID-19 vaccine safety surveillance rather than develop whole new systems from scratch.

COVID-19 vaccine safety monitoring has its own particular challenges [1]. In some settings the authorized vaccines are used interchangeably, with flexible dose intervals, often they were initially administered to elderly populations and those with high comorbidities. The reliance mechanisms between countries and regions cannot work if the vaccines used in low-to-middle income countries (LMICs) are different from those used in higher income countries (HICs). Also, unlike HICs, the populations receiving vaccines in LMICs can also be suffering from malnutrition and coinfections. In LMICs, the capacity to detect safety signals and adverse events of special interest is often limited. Decision-making about campaign rollout is challenging when new safety signals arise in a pandemic setting.

Most countries are investing their health budget in purchasing COVID-19 vaccines, without investing in additional pharmacovigilance activities or risk communication. Since the rollout of COVID-19 vaccination programmes, there has been a sharp rise in AEFI reporting which has inundated immunization programmes and regulators with work to evaluate and respond to these reports and to undertake the complex risk-benefit communication that follows.

At the World Health Assembly in November 2021, WHO called for recognition of the interconnectivity of our world and gave their commitment to support the One Health approach [2]. This approach aims to balance and optimize the health of people, animals and ecosystems through collaboration, coordination and communication to ensure effective capacity building. The COVID-19 pandemic can provide opportunities to improve pharmacovigilance using the same actions.

Regulators in many LMICs have switched to using online AE reporting tools and short message service (SMS) systems to prompt vaccinees to report any adverse effects. Active surveillance projects such as pregnancy registries, data linkage studies and cohorts are being used to obtain much needed data on the safety of the vaccines in high-risk groups. In addition, additional expertise has been added to national AEFI causality assessment committees with better co-ordination between regulators, public health programmes and other stakeholders to respond to signals. Initiatives such as the Brighton Collaboration worked collaboratively to rapidly develop case definitions for new AESIs [3]. We are quickly learning the importance of framing messages around harm in the context of benefit, using new platforms and approaches to communicate these messages, recognizing the need to build expertise in risk communication while building our capacity to actively engage with those who have concerns about COVID-19 vaccination.

Global collaboration in pharmacovigilance is facilitated through virtual meetings. During the COVID-19 pandemic this has offered an opportunity to improve worldwide coordination to address key pharmacovigilance challenges and to develop shared objectives for pandemic pharmacovigilance. Regulatory agencies are working to improve connectivity between safety monitoring and risk management plans across pre- and post-marketing phases.

Communication with smartphones due to their widespread use, even in LMICs, has facilitated online reporting, training and awareness building and remote diagnosis of conditions in settings with limited

access to the relevant clinical expertise. Social media platforms can be monitored to identify sources of misinformation as well as safety concerns that need to be addressed with factually-correct information using the very same platforms. We have only just begun to appreciate the impact of these tools in promoting safety of medicinal products, but as we are competing for limited attention, we may not always realize the full benefits of these platforms.

Various regional initiatives, e.g., the African vaccine regulatory forum can be used to address shared safety surveillance imperatives. Clinician networks and telemedicine tools have helped people in the front-line to deal with therapeutic challenges. They offer a perfect opportunity to support real pharmacovigilance feedback where it is most needed.

Lastly, we need careful logistics planning to minimize the impact of these large-scale vaccination programme rollouts on animal health and the environment, in line with the One Health commitment. For example, we need to organise safe waste management, including the safe incineration of unused or expired products. However, all efforts to build collaboration and communication must be underpinned by good science, transparency and explicit acknowledgement of uncertainties.

Going forward, we can use the lessons learnt during this pandemic. There are some elements of this type of crisis that can be predicted and therefore it is possible to be prepared. For example, ensuring that we have the coordination, communication and collaboration channels in place, so that regulators speak to each other and that there is a mechanism for this. WHO has played an important role in this by facilitating exchanges between regulators, government departments and other stakeholders. Having mature reliance mechanisms, with transparent communication between regulators in LMICs and HICs would also contribute to the preparedness.

Infodemic management during a pandemic

An infodemic does not only occur with misinformation, but it also occurs when huge amounts of information are generated, as with the current COVID-19 pandemic. It spreads between humans like infection during an epidemic, via digital and physical information systems, making it hard for people to find trustworthy sources and reliable guidance when they need it. Information overload occurs and contradictory information is disseminated. Because people are so connected, the information often travels faster than our ability to respond, which is a challenge for public health services. Infodemic management is not only needed during emergencies, but it is also needed in non-emergency situations so that health systems can use evidence-based approaches to communication and other activities to support behavioural change. If this is done correctly it will create an enabling environment which can, in the event of emergencies, facilitate higher acceptance of public health and social measures and of vaccines or other treatments.

Infodemic management needs to start with understanding concerns of different communities and their questions. This will inform not only how we should communicate, but also about how we should deliver the vaccine. For the communication we need to be present where the conversations are taking place, in a safe space that will allow individuals to ask questions and discuss these serious topics. Health authorities need to have other mechanisms in place to communicate about the factual aspects of the science. Long-term interventions and tools that are needed to help to build resilience to misinformation are being tested by WHO in collaboration with the scientific community.

WHO has invested in technology for digital real-time on-line listening to people's concerns and questions (see the next section). The information gathered can be combined with information from pharmacovigilance and health systems to inform actions on changing health behaviour.

Understanding that people have multiple personalities and, therefore, understanding what matters to them in different situation is important. Analyses of their sentiments and emotions, using quantitative and qualitative methods will help to development communication that will be more effective.

The Peek Platform: an early warning system for COVID-19 vaccine-related events

WHO have developed an open-source monitoring tool, the Peek Platform, which is part of a signal Early Warning System. This platform leverages artificial intelligence to detect, identify and classify COVID-19 vaccine-related events from online discussions. The platform collects data published on Internet or available from public social media platforms and news outlets with a focus on COVID-19 vaccines and potential vaccine-related events in English, Spanish and Russian. Despite the language restriction, there were over 175 000 documents on COVID-19 vaccines and side effects published daily in November 2021, with about one-third being Web articles. It is estimated that it would take a person 145 days non-stop to these documents.

The Peek Platform uses a transformer language model that can identify subtle differences in sentence construction. For example, 'the sheriff received his first shot' would be classified as a vaccination event, but 'I shot the sheriff' would not. The smart algorithms help to improve the recall-precision trade-off, by detecting sufficient documents to optimize the loss of any important vaccine-related events and the amount of background noise. The Peek Platform is part of a larger initiative to monitor potential COVID-19 vaccine safety signals. An example of how this can work is shown in the figure below.

In Thailand, the vaccination programme involves a second dose of the Astra-Zeneca vaccine after a first dose of the Sinovac vaccine. On 21 July 2021, a report about a death following this second dose was detected and investigated immediately. This rapid detection and reaction allowed a news item to be published nine days later concluding the death was a coincidental event, unrelated to the vaccine, thus avoided a potential communication void that could have been filled by misinformation. The Peek Platform has also picked up vaccination-related errors due to, for example, wrong vaccines being administered, wrong dilutions, and administration of expired vaccine. Their detection enabled the vaccination procedures to be refined so as to prevent similar errors in the future.

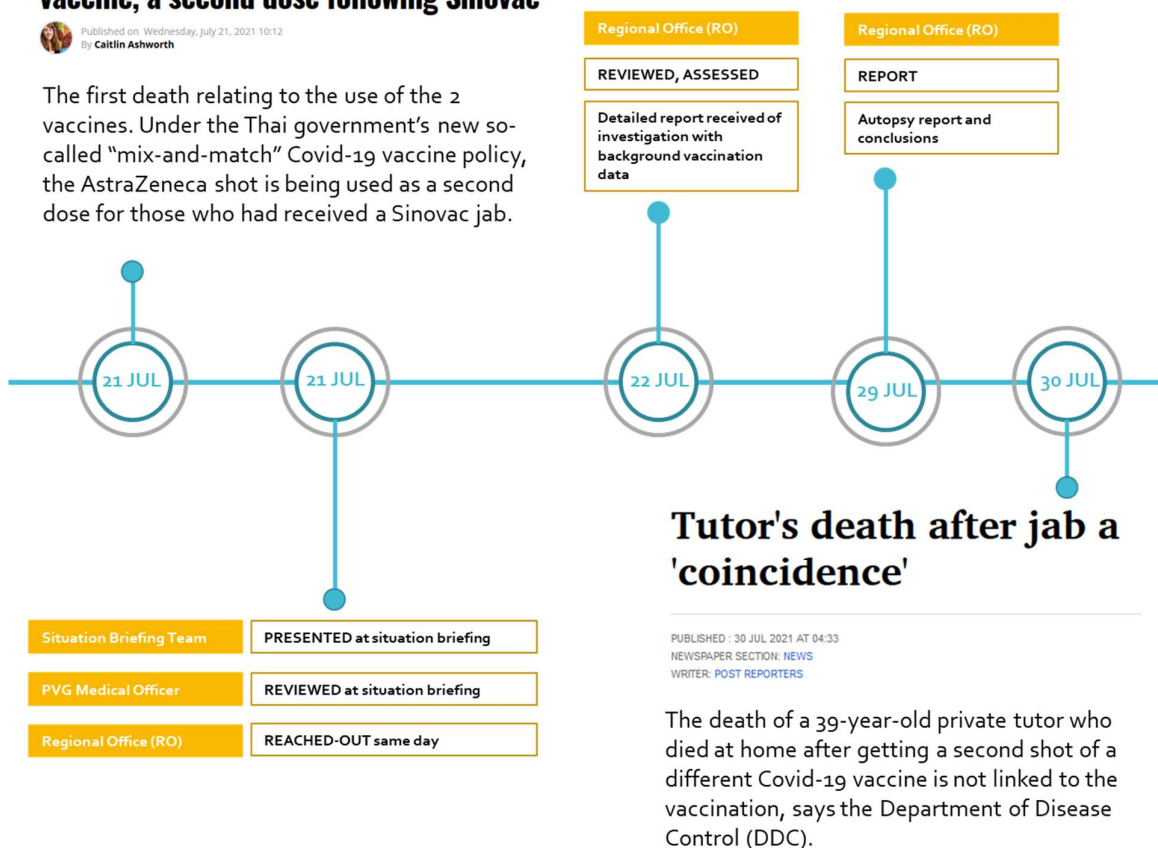
The Peek Platform can be used to identify unknown symptoms that are discussed on social media. A symptom does not have to be mentioned many times to be picked up, showing the sensitivity of the platform. For example, out of almost 215 000 people discussing their personal accounts on social media, almost 3000 talked about side effects. Among these 20 talked about insomnia which was mentioned 209 times and was most frequently mentioned in association with the BioNTech Pfizer vaccine. There were also four people who talked about diarrhoea which was mentioned 210 times and was most frequently associated with the Sinopharm vaccine.

39 year old dies after AstraZeneca vaccine, a second dose following Sinovac



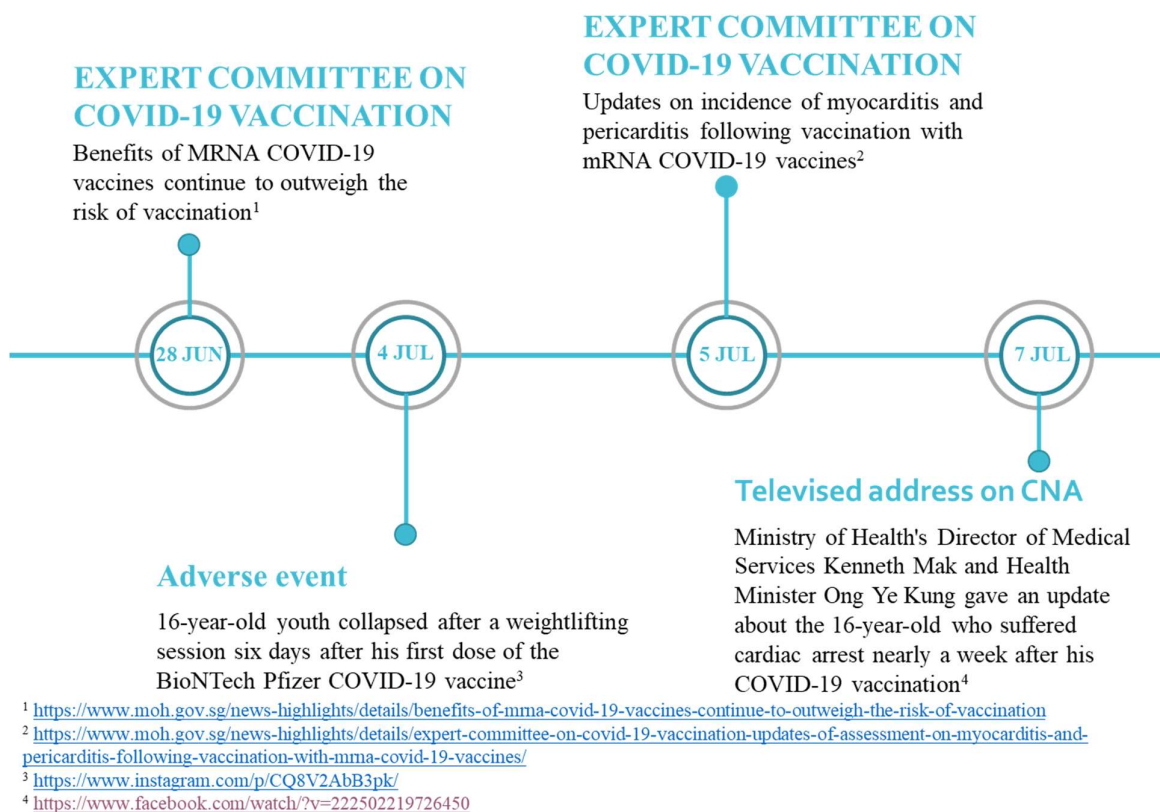
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By Caitlin Ashworth

The first death relating to the use of the 2 vaccines. Under the Thai government's new so-called "mix-and-match" Covid-19 vaccine policy, the AstraZeneca shot is being used as a second dose for those who had received a Sinovac jab.



The case study below illustrates how, once the Peek Platform has picked up a signal in Singapore, other platforms that are part of the early warning system can be used to understand the impact of the signal and the outcomes. This can result in timely communication which can avert panic and distrust in vaccines and vaccination.

In Singapore, a 16-year-old male had a cardiac arrest after doing intense sport six days after having received his first dose of the BioNTech Pfizer COVID-19 vaccine. The next day the Expert Committee on COVID-19 Vaccination issued updated recommendations about avoiding exercise or strenuous physical activity for one week after vaccination. The Ministry of Health quickly updated and translated its infographics and shared it widely. The timely response created a library of content reinforcing the guidance from the Ministry of Health. CrowdTangle is a platform that can be used to search for content across Facebook and Instagram to help understand what people are sharing and consuming via these social media. This showed that the infographic from the Ministry of Health and the newspaper that reported the story performed better than the average post in terms of number of shares and comments. Pulsar, a social listening and audience segmentation tool based on artificial intelligence, is another platform that is part of the Early Warning System. The data collected showed a rapid peak in posts and engagements (i.e., interest in the topic) two days after the event, indicating high interest, and then a sharp decrease as people tend to post topics that will receive attention. The overall sentiment about the post was negative, due to the topic, and more than 70% of males repeated the government recommendations, thereby placing the responsibility on the young male for having exercised. These insights into different responses can help organizations to tailor their communications to strengthen positive behaviour towards official messaging and guidelines.



In addition, the Early Warning System described here could be used outside of pandemic settings by following, for example, topics related to specific medicinal product.

Processing and assessment of individual case safety reports using artificial intelligence

Individual case safety reports (ICSRs) contain information about an individual, the adverse event, the suspected medicinal products and the reporter. Artificial intelligence (AI) has been defined as the science and engineering of making intelligent machines, especially intelligent computer programmes [4]. Machine learning (ML) and natural language processing (NLP) are two AI technologies that have been used to process and assess ICSRs [5, 6].

ICSRs are a more tradition source for the identification of new safety issues and information, especially for rare events. The growing volume of ICSRs, particularly for the medicinal products used for prophylaxis and treatment of COVID-19, is a challenge for their timely processing and assessment. ICSR processing involves intake, evaluation, follow-up and distribution, with each activity involving several subprocesses, making its computable difficult [7]. Intake requires the identification of four minimum data elements [8]:

- an identifiable reporter
- an identifiable patient
- an adverse reaction, and
- a suspect product.

Other relevant information also needs to be available. Additional steps involve determining the seriousness of the adverse event, its expectedness i.e., already in the product prescribing information, and for AEs from a study, the likelihood of a causal association [9]. The causality assessment still relies primarily on expert judgement, often using additional information. It is important when we look at how to use AI to note that a complete computable cognitive framework for this has not been developed because of the complexity of this activity.

FDA have developed a document primarily focused on AI and ML software as a medical device [6]. Although this does not apply to pharmacovigilance legally, there are many scientific principles that are common. For example, assessing algorithm performance e.g., validity, generalizability, absence of bias, and robustness in real world settings with changing inputs, is essential before implementing AI in pharmacovigilance. The algorithm development process must be documented and transparent to be able to understand why it makes its predictions, and quality control with real-world data collection and monitoring, and algorithm change control are all needed. The F1 score is one summary measure of the balance between recall and precision that can be used to assess algorithm performance compared with human experts. This score, which ranges from 0 to 1, should be close to 1 for full automation, i.e., use of the AI system's output without human review. How close to 1 is needed depends on the associated risk, for example, if misclassification by the algorithm were to lead to missing an important safety signal, a near perfect F1 score would probably be required. The acceptable level of the lower bound of an AI system's F1 score would depend on the context of its use. Outputs with an imperfect measure must be controlled by humans, so it must fit into the processes and workflows.

Some published examples of the use of F1 scores to assess the performance of an algorithm in different situations show that the scores can range from 0.36 to 0.91 [7, 10-13]. The results demonstrate that some aspects of ICSR processing and assessment could be done by NLP and ML algorithms to augment human expertise however, human-mediated quality assurance will be necessary for the foreseeable future. AI should be considered as a tool for supporting humans rather than replacing them. Automation could help to highlight existing inconsistencies in assessment processes, which could lead to general improvements in the processes. Current AI systems can contribute to improving ICSR case processing and assessment, but are not a panacea, and more scientific assessment and development of best practices in AI generally are needed before AI can be fully applied to ICSR processing and assessment.

Some of the challenges for using AI for routine processing and assessment of ICST cases include the specificity of the algorithms for specific systems, so we need to be able establish large, shared data sets to test the algorithms. Also, important information can be found in the narratives, which also contain personal health data, so the problems linked to confidentiality need to be addressed.

Disproportionality analysis of spontaneous reports

The number of ICSR reports received by Uppsala Monitoring Centre (UMC) since COVID-19 vaccines have been implemented is equivalent to the total number received in its first 40 years of operation. In the UK almost 400 000 spontaneous reports, with almost 1.3 million events, have been received up to 24 November 2021. Disproportionality analysis is used to assess if the number of reports for adverse events of special interest (AESIs) is higher than expected. For example, there were 494 reports of Bell's palsy for the BioNTech Pfizer vaccine, 598 for the AstraZeneca vaccine and 42 for the Moderna vaccine (and two for a non-specified vaccine). Bell's palsy represented

0.288% of all reports and therefore, applying the same proportion we would expect 393 reports for the BioNTech Pfizer vaccine, so the observed proportion is 1.26 times more.

This approach might be better if we use the proportion for all vaccines, not just COVID-19 vaccines, or the proportion for all vaccines and drugs to obtain a background expected proportion. This could be stratified by age or calendar year. This expected proportion could then be used to calculate either the proportional reporting ratio (PRR) or the reporting odds ratio (ROR) with 95% confidence interval or chi-square value. Bayesian methods, such as that used by UMC, i.e., Bayesian confidence propagation neural network (BCPNN) can be used [14]. Adding 0.5 to both the observed and expected is a simple method that improves results when the proportions are low. Another method is the multi-item gamma Poisson shrinker (MGPS) method used by the FDA and MHRA, but this is complex and most countries, particularly LMICs would not need to use this approach [15]. The sequential probability ratio test is a simpler method, which involves subtracting the expected from the observed [16]. These methods are, nonetheless, very similar and by adjusting the threshold for signal detection, similar results can be obtained [17, 18].

It would seem reasonable to assume that if a vaccine increases the risk of an adverse event, an increase in the disproportionality statistic could be expected in spontaneous reporting databases. Although differing degrees of agreement between ADR risk estimates from spontaneous reporting and formal studies have been reported, disproportionality analyses should not replace formal studies. [17, 19]. However, they could provide an initial indication of the likely clinical importance of an ADR, should the signal be confirmed subsequently. Therefore, how the expected proportion is estimated is important and currently, good practice recommends performing both approaches.

Confounding factors, such as age, should also be taken into consideration because the average age of those who receive the various COVID-19 vaccines are different. Coincidental events could be higher in certain populations, such as myocardial infarction in older individuals, and could be mistakenly identified as a signal.

Another approach could be to determine background rates from epidemiological studies or a database other than the spontaneous reports database. Exposure can also be determined from other databases, such as OpenSAFELY in the UK which has data for nearly 58 million COVID-19 vaccine recipients [20, 21]. Differences in vaccine coverage by characteristics such as age or ethnic group should be considered when assessing safety signals in spontaneous reports.

Data mining in pharmacovigilance databases for both vaccines and drugs is used primarily to detect signals. It can also be used to triage signals in situations like the current COVID-19 pandemic, where it is impossible to assess all reports. We should start with the assumption of no causal association between any vaccine or medicinal product and potential adverse events when processing signals. Signals of disproportionate reporting (SDR) measure departure from this assumption. When SDRs are detected, we may require extra information, e.g., delay between administration and event onset, to assess a causal relationship. It is also important to know if the reports are independent or not, since five reports from the same reporter does not have the same importance as five reports from different reporters.

Self-controlled studies can also be used for detecting rare events. A study in the UK showed increases in Guillain-Barré syndrome (GBS) and Bell's palsy in AstraZeneca COVID-19 vaccine recipients, but not BioNTech Pfizer vaccine recipients [22]. However, the increase in these events were greater after SARS-CoV-2 infection. The study also reported increases in haemorrhagic stroke

in BioNTech Pfizer vaccine recipients. After further assessments, the only event that was classified as a signal was GBS in AstraZeneca COVID-19 vaccine recipients.

Vaccine and drug safety evaluation is still challenging and despite progress we do not have all the answers about how to deal with individual issues and the methods for signal detection, evaluation and decision making. New statistical methods are needed for the current large volume of reports which should be combined with clinical expertise and wisdom to evaluate signals and take decisions. Electronic health records and other databases need to be harnessed to provide complementary data not available in the spontaneous reports and better collaboration is needed between those analysing spontaneous reports and those doing epidemiological studies to facilitate this.

Global pharmacovigilance databases – development and current challenges

Pharmacovigilance has come a long way over the past 40 years. Initially, decisions and recommendations were based on ICSRs, which were the only source for signal detection. These reports remain an essential source for signal generation, and although false positives are very unlikely, there is a real risk of false negatives. In this initial period, causality assessment was possible at the individual report level using a combination of expert judgement, algorithms and probabilistic methods, such as Bayesian statistics and logistic models. One of the main problems was underreporting and the lack of information about the total numbers of individuals exposed and background rates for the event. In the second period, drug sales statistics were available, making it possible to estimate exposure rates in the population. It was also possible to compare event risks between drugs. Statistical methods were developed to take into consideration possible differential reporting.

In the third period, large pharmacovigilance databases containing increasing numbers of ICSRs were available. This made it easy to compare event rates between drugs and to use disproportionality analysis, as described above. However, in larger databases, even small differences become statistically significant. Analyses of large databases can reveal more than 10 000 signals, which cannot all be assessed, therefore prioritization is required, based on, for example, potential population impact. UMC was a main player in developing these methods and thereby enable safety signals to be detected and analyzed.

Now, in the fourth period, we have access to large global databases, which are often primarily set up for costs and reimbursement systems. These databases contain sociodemographic data for the population covered and data about the healthcare professionals. They also contain healthcare data, such as consultations, diagnoses, hospitalizations and prescriptions. They do not contain data on over-the-counter drug use, indications for treatments, lifestyle habits or environmental exposures, which can be confounding factors. However, these databases increase the potential types of analyses that can be done. Precise estimates of risks can be obtained in subgroups, for example, by age. With these databases, the ‘sample’ is the whole population thereby providing all the data we need, and possibly, more than we need. Small differences can be ‘significant’ and require new analytical approaches which makes it difficult for regulatory agencies to make decisions.

For the future, we must find a way of ensuring that the sophisticated tools do not substitute for human expertise. For example, if an analysis shows that anti-psychotic drugs protect against COVID-19 disease it is possibly a valid result, but we need brains and good sense to put this into context. Individuals suffering from psychotic conditions probably have fewer contacts with other individuals and therefore have a lower risk of infection due to this, rather than the treatment they are

taking. So going forward, we must not forget that human expertise and reasoning is an essential element in assessment of potential safety signals.

The main objective of public health and pharmacovigilance systems is the protection of populations. The prioritization of signal processing should include rapid exploration of any signal that is medically and pharmacologically plausible if it is likely to have a significant impact on the population. Pro-active assessment of potential associations between vaccines and medicinal products that are widely used and common serious diseases should also be included. In the past pharmacovigilance systems identified rare, specific events, with a strong association with treatment exposure (relative risk >5) and a short delay to onset, but which had a low public health impact. Now the challenge is to assess more common diseases, with a longer delay to onset and a weaker association with treatment exposure (e.g., relative risk <2 or 3) because these could have an important public health impact if exposure was massive. This can be done with the larger global databases that are available.

Pharmacovigilance for COVID-19 vaccines and medicinal products

Although unmasking signals for vaccines and medicinal products for COVID-19 is a challenge in this pandemic setting, it can also be seen as an opportunity to innovate and adapt our signal detection methods. As of October 2021, nearly 575 million doses of vaccines have been administered in the European Union (EU) and European Economic Area (EEA), which should enable the detection of any rare side effects. Pharmacovigilance has been confronted with new real challenges for signal detection of unexpected events at both national and international levels. Pandemic preparedness has been key for the successful management of expected events. For example, the core requirements for COVID-19 vaccine risk management plans (RMPs) were developed to facilitate and harmonise their preparation and evaluation. For COVID-19 vaccines, there is a recognized need for observational post-authorization safety studies (PASSs) to assess identified and potential risks and to collect missing information.

The ACCESS project ('vACCine Covid-19 monitoring readinESS') has been success in identifying and characterizing a Europe-wide network of data sources that could be used to investigate specific research questions on COVID-19 vaccines and epidemiological methods to monitor the safety, effectiveness and coverage of COVID-19 vaccines [23]. One of its most important achievements was developing the mechanisms for estimating background rates of adverse events of special interest (AESIs) and other relevant conditions which are essential to those conducting observed vs expected analyses to assess spontaneous reports for specific AESIs. In addition, several national COVID-19 vaccine pharmacoepidemiological studies have been performed or are ongoing.

The major challenge for both regulatory authorities and the pharmaceutical industry is signal management based on spontaneous reporting. Member States have set up national systems to collect data, for example via national health data registers that collect information on individual vaccination exposure and the use of traceability tools such as stickers to allow for batch identification.

As of 28 October 2021, 428 million doses of the BioNTech Pfizer vaccine and 68.8 million doses of the AstraZeneca vaccine have been administered in the EU and EEA and there have been 412 571 and 214 528 spontaneous reports of AEFIs, respectively. The EMA has developed a detailed guidance document providing recommendations relevant to the processing and submission of ICSRs for COVID-19-related vaccines and medicinal products [24]. However, the system is overloaded with reports and their quality and completeness is not always optimal.

The EMA and national regulators propose that ICSRs for AESIs, and fatal or life-threatening reactions should be submitted within 15 days, when feasible. This has been challenging, especially when cases were reported rapidly in the media in some countries and assessed at a national level before being sent to the international network. Two challenging signals for unexpected events have been detected, i.e., thrombosis with thrombocytopenia syndrome (TTS), and capillary leak syndrome, but not detected during routine signal detection with disproportionality or observed vs expected analyses. They were detected by individual spontaneous reporting of suspected adverse reactions from some countries that triggered a signal at a national level, based on some well-documented cases. The clinical assessment of the limited documented cases was of high quality allowing appropriate signal management, which led to major regulatory actions and unprecedented media attention, followed by rapid research by academics, the pharmaceutical industry and regulatory consortiums to provide better understanding of the event of interest. Case definitions were also developed in collaboration with the Brighton Collaboration.

Lessons for signal detection in mass vaccination campaigns should be learnt from these examples. Routine signal detection methods seem to be insufficient to screen efficiently the high volume of ICSRs related to COVID-19 vaccines to detect unexpected signals such as TTS and myocarditis with mRNA vaccines. More efficient detection of unexpected signals could be possible if signals of expected AESIs for which good data on background incidence rates available, are excluded.

Leveraging the pandemic to improve pharmacovigilance

The current pandemic situation could be leveraged to improve pharmacovigilance systems by encouraging two-way collaboration between LMICs and HICs. We are living in a global world where it is increasingly true that no man is an island, and even local actions can have a global impact. HICs often do not serve the interest of this global world, as seen by the failure to deliver COVID-19 vaccines to LMICs and provision of pharmacovigilance systems. However, WHO and UMC has done a good job, not only with their database and data entry systems, but through training to build capacity in LMICs.

Changes to the way some people view reporting side effects are needed. Some people, particularly in LMICs, are reluctant to report these effects because they feel they are criticizing the medicinal product. In HICs there seems to be a better acceptance that any effective treatment can also have unwanted effects and an understanding of benefit-risk balances. Training, targeted communication and active encouragement to report events could change this. Access to technology, such as mobile phones, is high in LMICs. This technology should be used more widely to collect data on events. Healthcare professionals in LMICs often say “I reported it, but I didn’t hear anything back”. Mobile phone apps can and should be used not only to collect data but also to provide this important feedback, even on an individual case. We can see from social listening that reporting events is an emotional action for many people, so when we give feedback, we should use a human approach, showing recognition of the emotions, and not just provide numerical feedback.

Recommendations for moving forward

We are in an unprecedented situation where medicinal products (vaccines) have been developed in a short time and the target is not just a part of the population; the global population is targeted, i.e., 7 billion humans. Traditional pharmacovigilance systems were not designed for this workload, but they have managed to give at least a basic response to healthcare systems. This is an opportunity to

introduce the changes that are needed and to adopt new technologies described above. AI is a set of methods that need to be combined in a particular way to ensure that it can change effectively how we do pharmacovigilance. WHO is looking to start consultation in new technologies and methodologies for pharmacovigilance with the Member States. The organisation of national pharmacovigilance systems and cooperation with global systems is important to ensure regulatory agencies have complete oversight over the safety of medicinal products, not just for detecting safety signals but also their correct use.

It is time to move forward and we should not fear changes, we need to discuss them openly through a public consultation process to allow the whole community to voice their opinions. There are three potential actions that could help us move forward. Firstly, a working group should look at the limits of the disproportionately approach, identify additional data sources for pharmacovigilance and different methods adapted to specific settings. Secondly, another working group should look at the impact of signals, particularly in LMICs, and how they can be helped by providing support for processing the signals, taking into consideration their situation and their available resources. Thirdly, to be avoid reinventing the wheel, a mapping exercise of all regional, national, and international, public, and private initiatives should be undertaken.

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