Review Article

AN OVERVIEW OF PHARMACOVIGILANCE AND ADVERSE DRUG REACTION MONITORING OF DRUGS AND VACCINES DURING THE COVID-19 PANDEMIC

ABSTRACT

Once a drug is approved in phase III of clinical trials, pharmacovigilance (PV) becomes very important for the surveillance of drug, vaccine or medical devices. PV constitutes part of the phase IV approval, which involves a study for collecting, detecting, and monitoring adverse events in any population that the drug is used. The adverse events that are reported must be assessed to ascertain the causal effects and prevent or avoid unanticipated side effects on the population. With the advent of the coronavirus disease 2019 (COVID-19) pandemic, vaccination has been the motor for the management of the pandemic, and through intensive health sensitization, more people are vaccinated in a short period leading to greater challenges to the PV taskforce and the PV operating centrers. Global partnerships including the international society of pharmacovigilance (ISOP), the French national agency for medicines and health products safety (ANSM), and a multitude of others are working in synergy towards putting in place a continuous collaboration work package with many sensitization, education, capacity building, and research initiatives. This is within the framework of identifying the safety and efficacy of vaccines in order to provide solutions to emerging challenging ethical questions.
Through PV, signal detection is in progress for the identification of adverse events. The unanticipated emergence and negative impact of COVID-19, caused by the severe acute respiratory syndrome virus 2 (SARS-CoV-2) has significantly compelled global pharmacists and drug actors to collectively play an important role in the management of COVID-19. This has to be done within the framework of therapeutic strategies and guaranteed safety, efficacy and quality of new and old xenobiotics. In the current treatment COVID-19 has created health-related challenges and a shift in paradigm in drug discovery and development of new chemical entities (NCE), for vaccine or drug repurposing for different levels of treatment interventions. The accelerated interest in dynamic research and innovation have led to different approaches of treatment and this has come with potential side effects, which has led to the call for post marketing surveillance and monitory. PV is therefore a key component for phase IV study for the drugs and vaccines approved for global use. This paper gives an insight into the global PV monitoring and surveillance of new chemical entities (drugs and vaccines) and new technologies targeting the management of COVID-19.

Keywords: Pharmacovigilance, COVID-19, SARS-CoV 2, adverse drug reaction, surveillance, monitoring, vaccine.

INTRODUCTION.

Pharmacovigilance is the branch of drug development that deals with drug-related problems of detecting, monitoring and preventing drug adverse effects [1]. Patient safety is the main objective to achieve in PV, as multitudes of approved drugs have the potential problems of the risk of adverse reactions. Although in terms of risk/benefit ratio, the benefits of drugs/vaccines to the patient outweigh the risks, researchers must remain cautious of any serious side effect [2]. The PV monitoring of COVID-19 patients is an international priority for the Public health sectors. All health actors and organizations promote this activity in an effort to guarantee health transparency and monitor the benefit/risk of therapies being attempted or proposed for a specific validated treatment [3]. Based on the spontaneous notification requirement for the PV activity within the context of the pandemic, healthcare professionals are overwhelmed by the workload [4]. The specialized authorities are in need of active and comprehensive data collection from the different services receiving COVID-19 positive patients, of any suspected adverse effect that may be related to or associated with the use of any drug or vaccine [5]. This allows for the detection, analysis and evaluation of tolerance of the drugs prescribed. PV also investigates possible drug interactions resulting from drug combinations, underlying patient defects or related to the symptomatology and/or complications of SARS-CoV-2 infection [3,5].

1.1. The surveillance and monitoring of expected or anticipated adverse effects

The surveillance and monitoring of expected or unanticipated adverse effects may occur following the use of recommended drugs or drug combinations in the management of patients with COVID-19. This is necessary for the evaluation of tolerance and therapeutic responsiveness of the population [6]. Although the drug products and vaccines are now available for the management and treatment of COVID-19, these molecules are prescribed “off-label” in an unconventional treatment and administered to patients infected with a new SARS-CoV-2, where the physiopathology, evolution and complications are not yet well studied and characterized by inter-individual, genetic and ethnic variations [7]. These factors could affect the fundamental discussion of the risk/benefit ratio of treatments recommended for treatment in those conditions, and therefore considers other factors that could be of public health concern [8].

For identification and the approval of new chemical entities, all adverse events declarations of the COVID-19, the PV expert needs to collaborate with the units involved in the hospitalization of the patients within the population. More importantly, PV activity is aligned with the spontaneous notification of undesirable events related to the use of medicinal substances [3, 9].

1.2.**Types of notification for consideration in COVID-19 surveillance and monitoring**.

Based on the prevailing circumstances of the pandemic globally, many health authorities and sectors have advocated for surveillance and monitoring focused principally on two types of notifications:

1) The encouraged notification of inquiring each subject with the COVID-19 positive cases if they have observed any wanted adverse drug reaction.

2) The enhanced notification, in which the requirement for information on drug tolerance is referred to the medical officer. The notification document needs to contain the following essential elements:

- The Patient information: This consist of the first three letters of the patient's name (to guarantee anonymity), date of birth, sex, weight, and any history linked to the pathological conditions that may be a contributing factor to the adverse reaction. This information will allow mapping of the occurrence of the most common Adverse drug Reactions (ADRs) in target populations.
- Drug information: The different drugs that were used before the ADR and their dosage, the date on which they were first administered, the date on which the reaction first occurred, and the date on which the treatment was suspended or completed.
- The description of the suspected adverse event, the time of occurrence after starting the administration of the drug, the discontinuation of the drug (if applicable), restorative treatment (if applicable), and the notion of re-administration where applicable.
- The potential differential diagnoses, including data from examinations that have been performed.
- The associated factors that may increase the risk or predispose to the onset of the adverse reaction.
- The progress of the adverse reaction reported by the medical service [10, 11].

The evaluation of the scores related to the severity of the effect, as required by the Good Pharmacovigilance Practice, as well as in the legislation texts, cannot be effectively applicable following the pandemic situation. This can be attributed to the specificities of the COVID-19 subjects who are being managed, particularly in resuscitation and intensive care units [5, 12]. In addition, complications with the patients are added poly-pathological nature, with high-risk metabolic disease conditions like diabetes, hypertension, etc, and with a severe COVID-19 condition [13]. The criteria and the different aspects of the pathology of the COVID 19 itself is still not well understood and remain partially known to date. Furthermore, the contribution of drugs to the occurrence of certain clinical and biological activities seems difficult to understand, the link with the pathology, given the multiple drugs used in combination to treat patients with a serious diagnosed diseased condition. It is therefore proposed that an ADR is considered serious when it is an adverse reaction that is directly life-threatening, or result in a significant long-lasting disability or incapacitation [1, 14].

For others, the criteria of the evaluation of severity, which are prolonged hospitalization, has been discussed for its non-adaptation to the present circumstances, considering that the average length of hospitalization of a COVID-19 patient has not yet been estimated and validated. For the last criteria related to the occurrence of a congenital anomaly or malformation, there is a need for a multidisciplinary staff to discuss the balance of benefits of treatment for the mother and the foetus. The PV has the responsibility to then analyze the report and investigate the causal correlation between each symptom and each drug administered to the patient, using at least two standardized and harmonized methods of data inputs [15].

1.3. Drug classification according to the Anatomical Therapeutic Chemical Classification System (ATCCS)

The ATCCS classification system is a drug classification system that classifies drugs according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. Its purpose is an aid to monitor drug use and for research to improve quality medication use. It does not imply drug recommendation or efficacy [14]. It is controlled by WHO collaborating Centre (WHO-CC) for Drug statistics methodology), and was first published in 1976 [3, 9]

1.3.1. **Levels of Therapeutic and Chemical classification**

The most recognized therapeutic and chemical classification consists of 5 levels:

- 1st level: It defines the anatomical group.
- 2nd level: It defines the therapeutic or pharmacological sub-group.
- 3rd level and 4th level: They define the pharmacological, chemical, or therapeutic sub-group.
- 5th level: It specifies the chemical substance.

For harmonization of notifications, ADRs are coded in the database according to the Medical regulatory authority (MedRA) classification (Medical Dictionary for Regulatory Activities) [15]. This classification is organized into five levels ranging from the broadest to the most specific. The first level is entitled “System Organ Classes” (SOC), the second “High-Level Group Terms” (HLGT), the third “High-Level Terms” (HLT), the fourth “Preferred Term” (PT) and the last “Lowest Level Terms” (LLT) [9,16].

It allows an agreement of the standard terminologies used in vigilance flow (VigiFlow) systems [3, 16]. This is a web-based system for managing and reporting ADR cases internationally. In principle, notified and validated cases are transmitted to the national pharmacovigilance center *via* Vigiflow, which in turn forwards reports to the international pharmacovigilance center so that they can be centralized in the international vigilance-based (VIGIBASE) database. VIGIBASE is a World Health Organization pharmacovigilance database that has been in existence since 1968 and lists more than 8 million reports of Individual Case Safety Reports (ICSR) from various countries. Research and analysis of VIGIBASE are carried out using a search tool: Vigilyze™ [17]. This tool is used to describe and investigate adverse drug reactions on a global level. The analysis of adverse reactions reported with the drugs that are used for COVID-19 must take into account the context of risk association due to polymedication, associated co-morbidities and without exclusion of the COVID-19 disease itself, whose semiological and evolutionary criteria are not well understood [6, 18].

It is important to note that any causal relationship between drug intake and adverse reaction is established at a given time and may evolve depending on additional information for the effect that has appeared and/or the drug consumed [19].

The information on adverse reactions is crucial especially for the COVID-19 pandemic since its detection in 2019 by experts. Adverse drug reactions should be reported on a global scale so that

spontaneous action can be taken. The COVID-19 pandemic has created a huge impact on society. There is the need to safeguard the vaccine recipients and avoid unnecessary side effects [3, 20]. The adverse events reported was done from the first wave of pandemic [1]. Vaccine development data base Vigibase is maintained by the Uppsala PV monitoring centre. Vigibase constitutes the database of individual case reports that has been put in place to support in the prevention of spread of new coronavirus. Many vaccines of different types are under reporting by health care professionals for spontaneous infection [12, 21].

The national passive surveillance, for spontaneous reporting of suspected adverse drug reaction is most widely used to detect vaccine-related signals, in collaboration with healthcare professionals (HCPs) or patients/volunteers that spontaneously report the occurrence of safety and/or efficacy [22, 23]. The active surveillance method involves the collection of organized data at a particular point in time from vaccinated individuals who are participating in a study. The collaborations with international societies can facilitate in obtaining information with respect to suspected adverse reactions which could help in reducing unnecessary reactions in a large population [24]. The accessibility to real-life data is necessary for use in making treatment decisions and predicting outcomes. Continuous review of real-life data and events could provide information to the health care professionals on the safety of vaccines. Therefore, the collection of data from adverse drug reactions is also the objective of PV [4, 25].

1.3.2. The role of the International Society of Pharmacovigilance during COVID-19

The international society of pharmacovigilance (ISOP) in collaboration with the special interest group (SIG) was created to work as a team in identifying the safety and efficacy of drugs and vaccines for the prevention or treatment of coronavirus [26]. Some of the ISOP initiatives includes:

1) Monitoring drugs and vaccine publications related to COVID-19.
2) Provide support to regional pharmacovigilance societies.
3) Develop infographics and provide a global pharmacovigilance updates to health care professionals and patients.
4) To organize webinars in collaboration with drug safety organizations and actor.
5) To mentor and encourage other ISOP chapters and SIGs members to work and share their outputs with other team members.

The executive ISOP committee has to be in touch with individual ISOP members to provide support to the first-line workers. The main objective of ISOP is to provide professional and personal support. The support in low-income countries focuses on the management of challenges with limited resources [25, 27]. Sharing useful knowledge gained to the regional pharmacovigilance centres contributes to decreasing the burden of the people through campaigns and communication tools. Electronic health records and big data networks provide evidence to raised issues about drugs and vaccines [1, 28].

1.3.3. French organization for the pharmacovigilance surveillance and monitoring of COVID-19

The collaboration of the French national agency for medicines and health products safety (ANSM) in collaboration with the French pharmacovigilance network is effective to address valuable questions on the COVID-19 pandemic situation [7, 29]. French pharmacovigilance organization for COVID-19 vaccines surveillance is shown in figure 1. The pharmacovigilance of COVID-19 vaccine according to French organization is based on two dimensions [5, 6, 7].

1) An individual analysis of all real-time adverse drug reactions (ADRs) by regional pharmacovigilance centres (RPVc).
2) Conduct scientific analysis of all ANSM and RPVc experts.

The main objectives of French organization in COVID-19 are:

1) To detect signals in a fast and timely manner.
2) Show transparency in the safety of COVID-19 vaccine.
3) Provide weekly reports by experts to be made available on the French national agency for medicines and health products safety (ANSM) website.
4) Provision of response by health care professionals to patient request and seeking information about adverse effects of vaccines.
5) Assume responsibility within the territories in relation with the general public, health care professionals, hospitals, medical social institution.

1.4.Vigilance of COVID-19 vaccines

With the BioNtech/Pfizer COVID-19 vaccine, 74% of vaccinated women and 43% of the 50-64 years age group reported arterial hypertension, cardiac arrhythmias, Herpes zoster infection, thrombocytopenia, spontaneous hematomas, or a diabetes imbalance [30]. Five cases of severe hypersensitivity reactions were reported immediately. The above ADRs are rare but ADRs like fatigue, headache, nausea, fever, vomiting occurred due to the second dose in young adults according to clinical trial data [10]. Severe arterial hypertension (313 cases) was reported immediately or within a few hours or days after vaccination with or without the history of hypertension, which could be treated with anti-hypertensives or increasing dosage of pre-existing antihypertensive agents [8, 31].

With the Moderna COVID-19 vaccine, 74% of vaccinated women and 49% of the 75-84 years age group reported ADRs. ADRs like reactions at the vaccination site (pain, inflammation, cutaneous eruption), influenza-like syndrome (fever, chills, myalgia, arthralgia, asthenia), lymphadenopathy, digestive disorders and, hypersensitivity reactions. Delayed local reactions were reported 5- 10 days after vaccination [11, 32].

With the Vaxzevria COVID-19 vaccine, 74% of women and 72% of 16-49 years age group patients were mainly concerned with ADRs of Vaxzevria. Influenza-like syndrome association with dyspnea and asthma was reported. These cases are reported within 24 hours after the first dose. Twelve cases of thrombosis of a large vein associated with Thrombocytopenia and disseminated intravascular coagulation were reported [8, 33].

With the AstraZeneca/Oxford COVID-19 vaccine, the medicine and healthcare regulatory (MHRA) authority confirmed on 18th March 2021 that there was no evidence of blood clots caused by the vaccine, and benefits overweigh thrombotic risks [34]. The Medical health regulatory authority (MHRA) also stated that sinus vein thrombosis associated with thrombocytopenia has been reported in less than one in a million people vaccinated so far in the UK, and a causal association with the vaccine could not be established [12, 35]. The adverse reactions documented of COVID-19 vaccines reported cases are illustrated in table 1.

Table 1. Adverse reactions of COVID-19 vaccines [1, 3,8, 9, 21, 36, 54]

No	Approved Vaccine	Types of Vaccine	No. of admin doses	ADRs Reported in 2021	Clinical adverse events
1.	Cominarty BioNTech/Pfizer	mRNA	2	12,249 (25th March 2021)	Arterial hypertension, cardiac arrhythmias, herpes zoster infection, thrombocytopenia/spontaneous hematomas, diabetes imbalances
2.	Moderna	mRNA vaccine	2	577 (25th March 2021)	Delayed local reactions, facial swelling in persons with previous history of cosmetic filler injections., rheumatoid arthritis, peripheral edema/dyspnea
3.	AstraZeneca-Oxford vaccine group Covishield	ChAdOx1-S [recombinant] vaccine).	2	447 (17th Jan 2021)	Possible mortality with possible temporal relationship, 1 death associated with thrombocytopenia and stroke
4.	Janssen (Johnson and Johnson)	Viral vector Janssen Ad26.COV2.S COVID-19 vaccine	1	653, 35(11th June 2021)	Fainting events, Cerebral venous thrombosis
5.	AstraZeneca-Oxford vaccine group Vaxzevria	**Viral vectored vaccines**	2	743 (25th March 2021)	Influenza like symptoms, large venous thrombosis (cerebral, digestive), with thrombocytopenia or coagulation disorders, CVA, MI, PE, monoplegia, DVT, Ischemic stroke
6.	Sputnik V	**an adenoviral-based, two-part vaccine against the** SARS-	2	-	Deep vein thrombosis, cerebral circulatory failure, transient ischemic attack, vascular encephalopathy

		CoV-2 coronavirus. Initially produced in Russia in 2020, Sputnik V uses a weakened virus to deliver small parts of a pathogen and stimulate an immune response.			
7.	Convidecia™ The first of its kind authorized in China	Recombinant Novel Coronavirus Vaccine **(Adenovirus Type 5 Vector)** ("Ad5-nCoV", trade name:).	1	-	Serious nausea, drowsiness and rare neurological disorder

1.5.Vigilance of immune thrombocytopenia purpura after COVID-19 vaccination

Immune Thrombocytopenic Purpura (ITP) is an immune mediated disease that results in decreased platelet count caused by abnormal platelet production and destruction of platelets in the circulatory system [13]. This results in bleeding, bruise, petechiae, bleeding gums, or life-threatening bleeding. This is usually preceded by infection about 7-10 days before the onset of symptoms [13-15]. The pathogenesis of ITP is unclear but it may be due to molecular mimicry. hepatitis B, human papillomavirus, varicella, and diphtheria tetanus-pertussis (DPT) vaccines in children and adolescents, other constituents of vaccines like yeast proteins, adjuvants, and preservative diluents. Additives like aluminum hydroxide and phosphate used in vaccines to enhance immunogenicity will result in autoimmune inflammatory syndrome induced by adjuvants [5,13-16].

After Pfizer/BioNtech and Moderna COVID-19 vaccines, 36 cases of immune thrombocytopenic Purpura were recorded to the vaccine adverse events reporting system [17]. Immune thrombocytopenic Purpura cases (150) were reported postvaccination in the pharmacovigilance database stated by the British Medical Journal (BMJ) [18]. According to USFDA and CDC, the cases of ITP were few compared to the general population can be treated with corticosteroids and immunoglobulins [19]. Increased risk of ITP after COVID-19 vaccine administration, and response to treatment with standard ITP therapy, states that there is a possibility of an association between ITP and COVID-19 vaccine [20].

1.6.Vigilance of thrombosis and thrombocytopenia after COVID-19 vaccine

After the Janssen's COVID-19 vaccination, 6 cases of cerebral vein thrombosis (CVT) associated with thrombocytopenia in women of age group 18-48 years after 6-13 days of vaccination were reported [21]. This suspended its use in the European Union, South Africa, USA [22]. With the Vaxzevria vaccine, 269 thromboembolic cases were reported to Eudravigilance while 57 cases of cerebrovascular accident, 34 cases of myocardial infarction, 22 cases of pulmonary embolism, 31 cases of monoplegia, 15 cases of deep vein thrombosis, 11 cases of ischemic stroke, 1 case of dissemination intravenous coagulation, 53 cases of splanchnic vein thrombosis, 173 cases of cerebral vein thrombosis were also reported [23, 37]. Most commonly, these events have occurred in females and the Vaxzevria was suspended in Denmark and is recommended in the older age group in UK, Belgium, Italy, Spain, Germany, France, Netherland, Finland, Sweden. The pharmacovigilance Risk assessment committee concluded that benefits overweighed the risk.

In India with the Covishield vaccine, 3 deaths were reported with possible temporal relationships, and 1 death was associated with thrombocytopenia and stroke [24]. With Sputnik Vaccine 1 case of deep vein thrombosis, 1 case of cerebral circulatory failure, 1 case of transient ischemic attack, 1 case of vascular encephalopathy were reported. This was approved for emergency use in 62 countries. Currently, it is in use in Russia, Armenia, Belarus, Guinea, Hungary, Iran, Kazakhstan, Kenya, Laos, Lebanon, Nicaragua, Pakistan, Paraguay, Serbia, Syria, Tunisia, UAE, Venezuela [25, 38]. With Convidecia no reports of thrombosis were reported in phase 3 clinical trials [26].

1.7.The vigilance of facial paralysis related events after COVID-19

Facial paralysis cases were reported with mRNA Covid-19 vaccines (Pfizer/BioNTech and Moderna) in pivotal phase 3 clinical trials. For facial paralysis events with the vaccine group, 7 out of 35654 cases were reported compared with 1 out of 35611 cases who received the placebo group [10, 27, 39] though a causal relationship has so far not been established. Concerning mRNA Covid-19 vaccines, 133883 cases of adverse drug reactions were reported in the World Health Organization Pharmacovigilance database as of 9th March 2021. A total of 844 facial paralysis-related events were reported. Of which 683 cases were facial paralysis, 168 cases were facial paresis, 25 cases were facial spasms, 13 cases were facial nerve disorders. With Pfizer-BioNtech mRNA Covid-19 vaccine, 749 cases of facial paralysis-related events were reported and 95 cases of facial paralysis-related events were reported with Moderna mRNA Covid-19 vaccine as of 9th March 2021. Of the total 844 cases, 572 patients were females, the median age was 49 (39-63) years, and the time of onset was 2 days [28, 40].

1.8. Vigilance of cerebrovascular accident events after COVID-19

With the Pfizer/BioNtech COVID-19 vaccine, a total of 31,459 cases of adverse events were reported in the vaccine adverse event reporting system database (VAERS). Out of the 165 cases of CVA reported, 27 reports resulted in death. With the Moderna COVID-19 vaccine, a total of 29,913 cases of adverse events were reported amongst which 145 cases of CVA which resulted in 27 deaths. With Janssen's anti-COVID vaccine, a total of 6,751 cases were reported. A model Pharmacovigilance reporting platform as recommended by WHO is illustrated in figure 1**.**

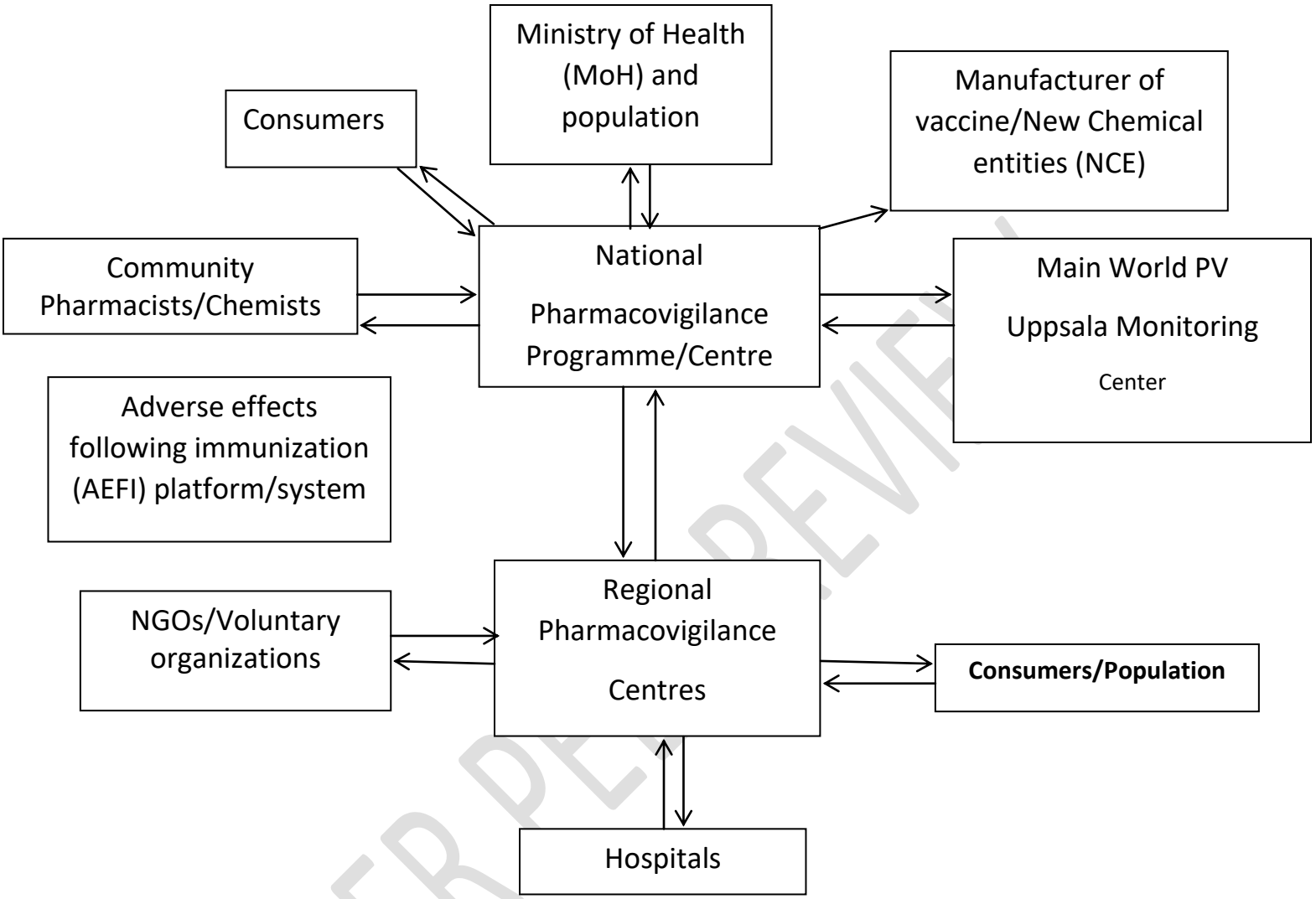

Figure 1. A model Pharmacovigilance reporting platform [9]

Deaths records after COVID-19 vaccination

As of January 8th, 2021, 6,688,231 individuals received COVID-19 Vaccines in India, and 55 deaths were reported, mortality rate was 8.2 per million populations [41]. When 6.93.246 residents of long-term care facilities were vaccinated, 37 deaths were reported with a mortality rate of 53.4 per million population. Among them, half of the reported 25 deaths were in the age group above 85 years. 14 individuals died immediately within a day and, 45 individuals died within 1 week after vaccination. Comorbidities associated with deaths were hypertension, dementia, chronic obstructive pulmonary disease (COPD), diabetes, and heart failure. Medications associated with this are pain killers, fever reducers, and antihypertensives [33, 42].

2.1. Role of pharmacists in COVID-19 management

Following the approval of vaccines against COVID-19, pharmacists are integral part in playing the role of primary frontline health workers in order to provide immunization to people, as demonstrated by community pharmacists who have been well-placed to provide accessible coverage in the past [43]. Furthermore, social distancing has obliged pharmacists to reorganize the way by which they dispense and give advice on medications such that, virtual consultations have become more popular, especially among vulnerable groups of the population [44]. In addition, the development of systems to provide drugs to patients is necessary to reduce non-essential medical and pharmaceutical visits and to maintain a good quality of service. Furthermore, some innovations have been introduced in many countries and they may be preserved in the future, that includes the electronic prescriptions with primary care, eliminating the legislative requirement for paper scripts [19, 45].

Pharmacists have an important role to play in supporting the health care system during this pandemic. Not only has this pandemic rendered new opportunities among pharmacies and patients, but also it has opened new avenues in the field of pharmacovigilance. Monitoring the efficacy and safety profiles of drugs constitutes a priority for healthcare professionals and patients, especially during the COVID-19 period for drugs administered to treat this infection in 'off-label use' [46]. There is currently a gap of information as data to create worldwide guidelines for the controlled and safe use of all drugs and vaccines administrated for the management of COVID-19 infection is insufficient; therefore, the increasing need and/ or to promote pharmacovigilance research is imperative [47]. It is important to control patient safety by rapid reporting of adverse drug reactions (ADRs). This aspect, for example, may be achieved by drug information services that provide 24-h professional advice to patients and healthcare workers after being exposed to drugs [13, 48]. Some hospitals are already in progress to evaluate the incidence, type and risk factors associate with ADRs among patients with COVID-19.

2.2. Impact of COVID-19 on the pharmacovigilance workforce

Due to the global challenges of COVID-19 pandemic that has cause socio-political instability, economic disruption, and the pandemic death and disability that have followed the novel coronavirus 2019 (COVID-19), there have been unexpected opportunities recognized by innovators, researchers and especially health care leaders, who have found themselves in the depth of caring for patients with COVID-19 [49]. Pharmacovigilance, too, may well be the beneficiary of unexpected opportunities during these periods. During the past 1 to 2 decades, PV has evolved as it has settled into three core disciplines-case management, signal management, and benefit-risk management-supported by professionals with distinct and gradually defined knowledge bases and skill sets [33, 50]. Furthermore, PV has played increasingly important roles in other domain-facing disciplines of pharmaceutical research and development, including nonclinical and clinical pharmacology, regulatory affairs, manufacturing, and medical affairs [51].

These evolving dynamics have been occurring against a backdrop of a long-term demographic slowing of population growth and ever-tightening availability of talent in all market sectors, despite the significant impact of COVID-19's forces on the business environment during the better part of the past years [52]. The knowledge bases and skill sets that are needed to support PV activities at these intersections has been identified. At the top level, these knowledge bases and skill sets fall into 2 basic types:

- Content-focused, which are generally performed by subject matter experts.
- Process-focused, which are generally performed by operational experts [53].

At the next level, developments in knowledge and skills have occurred in 2 parallel and mutually reinforcing components:

- Quantitative component, with greater emphasis on statistically based approach.
- Technological component, with increased emphasis on software platforms and artificial intelligence [54].

Large-scale change, historically driven by innovative new technologies and regulatory pressures, has generally occurred incrementally. However, the deeply felt effects marked by COVID-19 are forcing change at a very rapid rate. The scope of Pharmacovigilance domain of activities in the context of knowledge bases and skills sets needed to support these activities has been illustrated in table 2. If the knowledge bases and skill sets described in the Table 2 are viewed from a risk management perspective, most of the focus is on the front end, that is, on the detection/identification and analysis of pharmaceutical risks, activities that pharmaceutical companies can control. However, moving the focus to the back end, that is, on mitigation and communication of these risks, makes it clear that a significant shift is needed from quantitative and technological methods to soft skills, such as teamwork, collaboration, conflict resolution, and negotiation, all areas that require strong communication skills far beyond the immediate control of the pharmaceutical company, and into the pharmacy, clinic, and the patient's home environment.

The change in focus may open the way for the application of behavioral economics and other soft skill approaches that may have a more direct impact on improving patient outcomes and reducing patient harms. This may be "the middle of difficulty" in which lies the next opportunity.

Table 2. Scope of the Pharmacovigilance domain of activities in the context of knowledge base and skill sets needed to support these activities [39]

Domain of activities	**Knowledge base and skill settings**	
	Content-focused with subject matter experts	Process focused with operational experts
Main PV Disciplines/case management	Analytical/medical	Project management database Management,
Signal management	Systems analysis, medical, TSA, social media	Data management, social media Risk management
Benefit-Risk assessment	Risk: communication analysis concepts.	Risk: communication, project management
Other PV domain of related disciplines		
Animal pharmacology	Animal physiology, adverse event profiles, PK/PD profiles	Project management
Clinical Pharmacology	Animal physiology, adverse event profiles, PK/PD profiles	Project management
Regulatory/labelling	Global regulatory structures, risk communication, negotiation	Regulation, risk, communication
Clinical trials	Bioethics: consent, IRB, trial study design	

Manufacturing	Manufacturing process, quality: EMEA, SPC, security	Project management
Medical Affairs	Communication	
Data base management	Software, artificial intelligence	
Epidemiology/biostatistics	Quantitative methods, data analysis	
DMC=Data monitoring committee, FMEA=Failure mode effects analysis; IRB=Institutional review board; PKPD=Pharmacokinetics/pharmacodynamics; SPC=statistical process control; TSA=Time series analysis.		

3.0 COVID-19 vaccine innovation from traditional vaccine

3.1. The Nucleic acid and viral vectored vaccines

New innovative vaccines such as mRNA vaccines and viral vectored vaccines, including the Oxford ChAdOx1 nCoV-19 recombinant vaccine differ from many traditional vaccines through the way they activate the immune system [52]. In most traditional vaccines the antigen which is part of the disease that stimulates an immune response, are introduced directly into the body. On the contrary, the innovative types of the two newer approaches deliver the genetic instructions for the antigen to the body's cells. The cells then manufacture the antigen which goes on to stimulate the immune response [14, 53]. Injecting genetic material has raised questions about the use of these vaccines, such as whether they can modify the DNA of those receiving them. An explanation to demonstrate why this is not possible has been illustrated.

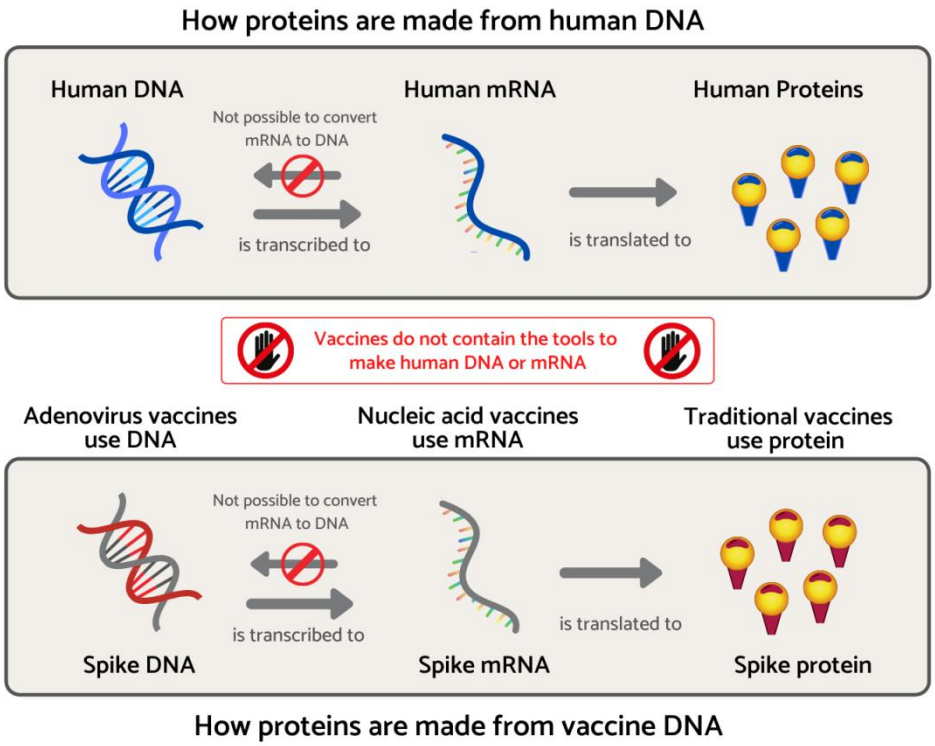

Figure 2. How proteins are made from vaccine DNA and RNA

We start by looking at how cells normally manufacture proteins. Our Deoxy Ribonucleic Acid (DNA) is safely packaged inside the nucleus of a cell and cannot leave. Within this DNA are gene sequences, and each gene encodes the blueprints for making one of the proteins the body needs [54]. To make a protein the first step is to transcribe DNA into messenger RiboNucleic Acid (mRNA), using a special enzyme (or "tool") called RNA polymerase. This step is a one-way process as cells are unable to transcribe RNA back into DNA [55]. Unlike DNA, mRNA is free to leave the nucleus as it has a pass that allows it to exit. However, this pass is one way and once it leaves, the mRNA cannot return. Once it has left the nucleus the mRNA links up with the special cellular machinery in the cytoplasm. This machinery uses the information coded in the mRNA to make new proteins [9, 56]. As with the process of going from DNA to mRNA this process is also one-way, and it is not possible to go backwards from protein to mRNA. These proteins may be used inside the cell or transported out of the cell for use elsewhere in the body.

The COVID-19 mRNA vaccines take advantage of this internal process to make copies of the spike protein, which usually appears on the surface of the coronavirus. There are two different types of mRNA vaccine (Pfizer and Moderna) which use this process:

3.2 mRNA vaccines

In this type of vaccine, mRNA is delivered to the cell inside a lipid membrane. Once the mRNA is inside the cell, the same machinery that is used to make our own proteins can make the spike protein [57]. This mRNA has no way of getting into the nucleus where the DNA is located. Even if it could, mRNA cannot fuse with DNA and as with our own mRNA, has no way of getting translated back to DNA. It is important to note that there is no way for human DNA to be altered by mRNA vaccine. This mRNA lasts a few days before the cell removes it, but in that time, it can produce a lot of spike protein to stimulate the immune response.

3.3 Viral vectored vaccines

Viral vectored vaccines work in a different way. The genetic information inside a viral vectored vaccine like ChAdOx1 is DNA rather than RNA. This DNA is a short linear piece of double stranded DNA which contains the viral genes along with the gene for the spike protein [58]. The viral vector first infects the cell and then delivers this DNA to the cell nucleus. The cell can then transcribe the viral genes into mRNA using the same RNA polymerase it uses for our own genes. After transcription, the mRNA gets tagged so it can leave the nucleus and be made into spike protein by the cell machinery.

In the Oxford vaccine, the viral gene that is required to replicate viral DNA has been removed. As viruses use a different process to human cells to replicate their DNA, the cell itself cannot replicate viral DNA either. This means the viral vector cannot replicate (make more viruses) or cause disease. Both the original viral DNA and the spike protein mRNA only last a few days before the cell removes them [59]. Such design features alongside a cell's natural DNA protection measures, prevents any possibility of viral DNA integrating with human DNA [41, 60].

4.0 WHO strategic platform on the pharmacovigilance study of COVID-19 vaccines

WHO in collaboration with Global advisory committee on vaccine safety GACVS held a meeting from the 1-3 December 2020 to hear an update on the vaccine safety surveillance plans of the European Medicines Agency and the United States Centre for Disease Control and Prevention, a review of the WHO COVID-19 vaccines safety surveillance manual, an overview of the recommended list of adverse events of special interest (AESI) for COVID-19 vaccines and feedback on the proposed template protocol for surveillance of these AESI. The Committee also

discussed the procedure for reviewing the safety profile of COVID-19 vaccines. The following salient themes emerged from the robust discussion.

Europe and the USA appear to be well positioned to implement vaccine safety surveillance programmes of unprecedented magnitude [61]. Concern was expressed, however, that low- and middle-income countries (LMIC) might find it more difficult to implement some of the studies that are being designed in Europe and the USA.

The COVID-19 vaccine safety surveillance manual was developed by working groups led by the Global Advisory Committee on Vaccine Safety (GACVS) members and other experts with diverse expertise from all WHO regions. A first draft was submitted for public consultation in early October 2020. All comments were reviewed, and the document was revised accordingly. The aim of the manual was to guide the processes for collecting, analyzing and sharing safety data and information on COVID-19 vaccines within and across countries [62]. It builds on the principles described in the Global Vaccine Safety Blueprint (GVSB), the WHO global manual on surveillance of adverse events following immunization, and the Council for International Organizations of Medical Sciences (CIOMS) guide to active vaccine safety surveillance [63]. For ease of use, the manual is divided into an executive summary and nine modules that can be consulted individually and which contain hyperlinks to relevant sections of other modules. The manual is available on the WHO website with relevant training materials and will be updated as frequently as required.

4.1 COVID-19 vaccines in the pipeline and potential safety issues

The strategic advisory groups of experts (SAGE) on immunization, is establishing a working group on COVID-19 vaccines to review the evidence on candidate vaccines, provide guidance for prediction models to determine the optimal target age groups and populations, update target product profiles and prepare policy advice for SAGE on accelerated use of vaccines, early allocation of limited vaccine supplies, equitable access to vaccination and vaccine safety. It is expected to issue its initial policy advice in October 2020. The usual timeline for vaccine development has accelerated markedly, and it is hoped that it will be reduced to the minimum feasible, namely 12–18 months. This will require assessment of risks and benefits, securing funding and emergency licensing approval worldwide and scaling up manufacturing capacity at the same time as vaccine development, rather than sequentially [45].

Seven vaccine technology platforms were earlier considered for COVID-19 vaccine development: live attenuated virus, inactivated virus, virus vector, virus like particles, protein subunits, mRNA and DNA [3, 27]. Most vaccines in development are based on protein or viral vectors. Only the live attenuated and vector-based vaccines can be delivered as a single

vaccination rather than as a primary vaccination with one or more booster doses. WHO and the London School of Hygiene and Tropical Medicine publish frequently updated summaries of vaccine development [39]. Twelve candidate vaccines entered phase I and/or phase II clinical trials by the end of May 2020. A Chinese recombinant adenovirus type-5 vectored vaccine was shown to be tolerated and immunogenic in humans 28 days after vaccination [5], while the University of Oxford–Astra Zeneca chimpanzee adenovirus (ChAd)-vectored vaccine showed good results in animal testing, although the reduced prevalence of SARS-CoV-2 in the United Kingdom was complicating the clinical trial in humans. Animal testing is in progress in parallel with phase II trials, and both public and private developers report to the WHO working group on animal models.

Information about the adjuvants used in the candidate vaccines is available only from individual manufacturers, and new adjuvant systems are being developed. A number of vaccine developers have committed themselves to making licensed adjuvants available for use with novel vaccines developed by others. GACVS members need to be kept informed of the activities of the SAGE working group and noted the need for guidance on compassionate use of the earliest vaccines before formal licensure, in line with WHO guidance on emergency use listing. GACV has also drawn attention to possible beneficial, non-specific effects of existing vaccines with a proven safety profile, e.g. BCG and measles vaccines. They further stressed the importance of effective public communication and of obtaining as much information as possible from the trials being conducted by private-sector vaccine developers [61-63].

4.2. Adverse events of special interest in the context of COVID-19 vaccine

Identification and assessment of adverse events of special interest (AESI) are of high priority, because, when their frequency after vaccination increases, they represent potential risks, which will change in the benefit–risk balance of the vaccine or may require prompt communication with the public by regulatory or public health authorities [11, 29]. Designating an event as an AESI has the advantage that countries can then prepare, with case definitions, collect information on background rates, collate relevant scientific literature, set up collaborations with relevant partners and establish platforms and strategies to assess signals rapidly. When a signal is identified, it might have to be investigated further through active surveillance, such as in risk quantification studies, hospital-based monitoring, population-based studies with large health care databases and reviews of various data sources, such as electronic health records, claims data and other sources of health care data [41, 56]. Since 2000, the Brighton Collaboration has issued over 60 case definitions for “adverse events following immunization” (AEFI), with 3 levels of

evidence, which provide guidance on collecting and reporting harmonized data on vaccine safety.

4.3. Benefit–risk assessment

The Brighton Collaboration Viral Vector Vaccines Safety Working Group (VSWG) was established in 2008 to allow stakeholders to anticipate potential safety issues, interpret safety data and improve public acceptance of vaccines. The Group has developed standardized templates to facilitate the communication of complex information, increase transparency and comparability and serve as a checklist for risk management [2, 8]. These templates assist national regulatory authorities and other stakeholders in assessing the benefit–risk profiles of specific vaccines. Three viral vector vaccine templates have been developed to date, with information on the wild-type virus, the viral vector itself and the final recombinant viral vector vaccine in animals and humans, its toxicology, potency and an overall assessment of adverse events and risks [15, 21].

As many candidates COVID-19 vaccines are not based on a viral vector. The Brighton Collaboration Viral Vector Vaccines Safety Working Group (VSWG) prepared templates for RNA/DNA, protein subunit, inactivated vaccine and live attenuated vaccine platforms, as well as a module on maternal vaccination [21, 36]. The templates include information on adjuvants, where appropriate. The templates are available on the Brighton Collaboration website.

4.4. Leveraging the 3 levels of WHO and its global partners for pharmacovigilance preparedness

WHO has pooled information from its regional offices about the lessons learnt from the epidemics of H1N1 influenza and Ebola virus disease. The regional offices and global partners can thus support countries in planning vaccine use and safety [36, 41]. National immunization programmes and national regulatory authorities must be prepared to collect information on AESI, independently of their link with vaccination. This may place an additional strain on already overstretched programmes in some countries, and WHO regional offices could reduce the burden on countries by organizing work-sharing and information exchange with other countries in the region [45].

The action necessary for vaccine safety preparedness at global level includes monitoring the safety and benefit–risk profile of COVID-19 vaccines, disseminating case definitions and ensuring a syndromic approach to the identification of safety signals and theoretical concerns,

guiding national plans to respond to safety signals in a robust, efficient manner [47, 52]. A preparedness plan for introduction of the COVID-19 vaccine must be developed at regional level, with a synchronized surveillance system for AESI and AEFI, engagement with vaccine safety experts and effective management of vaccine hesitancy, risk communication and issues of demand.

Each country needs to have a framework plan for introducing COVID-19 vaccination, and the risk management plan recommended by the national regulatory authority to be implemented and communicated, including active and enhanced passive AEFI and AESI surveillance nationwide [54]. Target populations for initial introduction and special population need to be identified, and safety surveillance should be established for these groups. Guidance on monitoring the safety of COVID-19 vaccines should be available at all levels. Vaccine hesitancy and the expectations of various constituencies should be anticipated and managed from the perspective of vaccine safety [39].

National preparedness for vaccine safety must be aligned with vaccination strategies, risk management plans and national AEFI surveillance, and pharmacovigilance should be adapted to include both available data and emerging information [8, 45]. Stakeholder engagement can be strengthened by defining their roles, by including risk communication in the preparedness and response plan and establishing a database of scientific literature from low- and middle-income countries [21, 36]. The ability of national regulatory authorities to evaluate safety and efficacy and to license novel vaccines should be strengthened. The roles and responsibilities of all stakeholders in planning, data collection, analysis and reporting on AESI must be clearly defined. National and international collaboration and exchanges of information are key aspects of effective management of vaccine safety [54]. Specifically, for vaccination against COVID-19, the maturity of the existing AEFI surveillance system should be assessed, and routine AEFI surveillance that may have been interrupted by COVID-19 activities and other challenges should be reactivated and/or strengthened. The vaccine safety preparedness plan, response plans, the necessary infrastructure (including cold-chain capacity at all levels), capacity-building, procedures for recording vaccination, quality assurance and sharing of data should be prepared and established before vaccine deployment.

CONCLUSION

Pharmacovigilance is important after drug, vaccine or medical device approvals as a phase IV study, for collecting, detecting, and monitoring adverse events in populations where the drug is used. The adverse events reported should be assessed in order to know the causal relationship and reduce or avoid unnecessary side effects on the population. With the emergence of the

COVID-19 pandemic, vaccination has become the driving force for managing the pandemic and more people are vaccinated in a short period, which has become a challenge for pharmacovigilance experts and centers. The international society of pharmacovigilance, the French national agency for medicines and health products safety, and many others are now in continuous collaboration and taking many sensitization and education/research initiatives to identify the safety and efficacy of vaccines to provide answers to the raised questions.

Pharmacovigilance remains a key element for phase IV studies after drugs and vaccines are approved for global use. After getting approval from the national immunization technical advisory group, vaccines are released into the market. Thus, pharmacovigilance helps in the detection, assessment, understanding, and prevention of adverse events following immunization. It eventually reduces the burden on public health.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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