DRUG SAFETY MONITORING FOR COVID-19: LESSONS FROM PHARMACOVIGILANCE AND GLOBAL STRATEGIES

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Abstract

The COVID-19 pandemic due to the SARS-CoV-2 virus accelerated the fast-tracked development and availability of therapeutics and vaccines for the mitigation of its devastating effects. The unprecedented speed of research, clinical trials, and EUAs gave rise to novel challenges in ensuring the safety and efficacy of medicines and hence pharmacovigilance became an integral part of the response to the pandemic. This project reviews the frameworks, methodologies, and challenges involved in the monitoring of the safety of COVID-19 vaccines and therapeutics with special focus on key lessons learned that could impact pandemic response in the future. Monitoring the safety of drugs during the pandemic employed a multi-faceted strategy involving pre-marketing clinical trials, post-marketing surveillance, spontaneous reporting schemes, and evaluation of real-world evidence (RWE). Adaptive approval schemes were employed by the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), and World Health Organization (WHO) to find a balance between urgency and safety requirements. Pharmacovigilance infrastructure like the Vaccine Adverse Event Reporting System (VAERS) and EudraVigilance played a crucial role in detecting and assessing adverse drug reactions (ADRs) and adverse events following immunization (AEFIs). The project evaluates the safety profiles of some key COVID-19 therapeutics like antivirals (remdesivir, molnupiravir, nirmatrelvir/ritonavir), monoclonal antibodies (casirivimab-imdevimab, sotrovimab), and immunomodulators (dexamethasone, tocilizumab, baricitinib) and their respective ADRs and post-marketing surveillance results. Additionally, vaccine safety monitoring analysis involves mRNA vaccines (Pfizer-BioNTech, Moderna), vector-based vaccines (AstraZeneca, Johnson & Johnson, Sputnik V), and inactivated vaccines (Covaxin, Sinopharm, Sinovac). Population-related problems, continuous safety monitoring, and new topics like autoimmune and inflammatory risks are also addressed. Key takeaways from COVID-19 pharmacovigilance are the requirements for near-real-time monitoring of safety, the use of digital health technologies (artificial intelligence, large-scale data analytics, and blockchain) in streamlining drug safety control, and the requirement of open public communication to rectify misinformation. Although the pace of the rollout of COVID-19 interventions proved the success of global cooperation in pharmacovigilance, issues like underreporting, heterogeneity of regulation, and public distrust show areas for enhancement. The project concludes with recommendations to enhance global pharmacovigilance systems, standardize international reporting systems, and revise regulatory pathways for potential future public health emergencies.

Key Words: COVID-19, Drug Safety Monitoring, Pharmacovigilance, Special Populations, Real-Time Surveillance.

1. INTRODUCTION

The COVID-19 disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in late 2019 and rapidly spread globally, leading to high morbidity and mortality [1]. The speed of spread and high mortality in some groups necessitated the immediate deployment of treatments and vaccines, among other interventions. The unprecedented speed of scientific investigation and regulatory approval provided challenges to ensuring the safety and efficacy of drugs, thus making pharmacovigilance an integral component of the pandemic response [2]. The World Health Organization (WHO) declared COVID-19 a pandemic in March 2020, which has resulted in over 700 million cases and over 6.9 million deaths worldwide as of early 2024 [3]. The virus is primarily transmitted by respiratory droplets, direct contact, and airborne transmission in closed spaces [4]. Symptoms of disease range from mild influenza-like to severe pneumonia, acute respiratory distress syndrome (ARDS), and multi-organ failure [5]. With the rapid mutation of the virus, especially with the emergence of variants with increased transmissibility and immune evasion, public health interventions have been dynamic to reduce transmission. Such interventions include lockdowns, use of face masks, social distancing, and mass vaccination [6]. Despite the prevention of severe disease and death by vaccines, concerns of adverse effects and long-term safety remain, with constant surveillance required [7]. The speed of spread of COVID-19 accelerated the research and development of therapeutic drugs and vaccines, with some receiving emergency use authorization (EUA) within months [8]. The traditional vaccine development time of 10 to 15 years was considerably reduced to less than a year because of the advancements in mRNA technology, adenoviral vector technologies, and protein subunit vaccines [9]. Several therapeutic medicines, including remdesivir, dexamethasone, and monoclonal antibodies, were repurposed or newly developed to be used for treating COVID-19 patients [10]. Antiviral drugs like molnupiravir and nirmatrelvir/ritonavir were approved based on early clinical trial data showing their ability to reduce hospitalization [11]. Although they were shown to be helpful, fears about safety, drug-drug interactions, and adverse events became inevitable, necessitating stringent post-marketing surveillance and gathering of real-world evidence [12]. The rapid deployment of vaccines, including those developed by Pfizer-

BioNTech, Moderna, AstraZeneca, and Johnson & Johnson, relied on novel platforms and emergency use approvals, leading to skepticism about long-term safety, rare adverse effects, and durability of immune protection [13]. The occurrences of VITT, myocarditis, and anaphylactic reactions necessitated continuous pharmacovigilance systems to be in place. The global regulatory agencies, including the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the World Health Organization (WHO), have put in place stringent safety surveillance systems to assess adverse effects and modify guidelines accordingly. Lessons learned from the rapid development and deployment of COVID-19 therapeutics and vaccines highlight the pivotal role of stringent pharmacovigilance systems, global cooperation, and adaptive regulatory policies in managing future pandemics and maintaining the trust of the public in medical interventions [14].

1.1 Importance of Drug Safety Monitoring

Role of Pharmacovigilance During Pandemics

Pharmacovigilance can be described as the science process as well as undertaking of identifying detecting, assessing, monitoring, and preventing adverse effects or risky phenomena which are associated with medicinal products. any other drug-related problems . In general, pharmacovigilance is very important at any time, but during pandemics, their importance increases because need for new drugs and vaccines deployed at an accelerated pace. The main objectives of pharmacovigilance during pandemics include in table no.1.

Table 1. Pharmacovigilance Objectives During Pandemics

Objective	Description
Monitoring ADRs & AEs	Continuous tracking of adverse drug reactions (ADRs) and vaccine-related adverse events (AEs) to ensure patient safety.
Identifying Rare or Long-term Side Effects	Detecting side effects that may not have been apparent in clinical trials, especially those with long-term implications.
Ensuring Transparent Communication	Facilitating clear and open communication among regulatory agencies, healthcare professionals, and the public.

Supporting Regulatory Decisions	Providing real-time safety data on new treatments to help authorities make informed regulatory decisions.

The COVID-19 pandemic demonstrated the necessity of real-time pharmacovigilance, enabling quick responses to emerging safety concerns such as myocarditis linked to mRNA vaccines and thrombotic events associated with adenovirus-vector vaccines [15].

Unique Challenges in COVID-19 Drug Safety Monitoring:

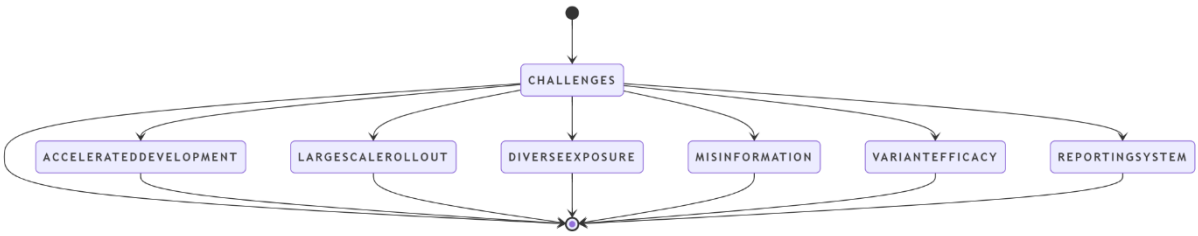

Figure 1. Unique Challenges in COVID-19 Drug Safety Monitoring

Figure 1. has outlined some of the challenges involved in detailing monitoring of drug and vaccine safety that was applicable during the COVID-19 period. The surveillance of drug and vaccine safety in connection to COVID-19 was a process accompanied by certain specific and profound challenges. First of all, due to the need for fast development and fast approval of the new, effective treatments, the regulatory bodies provided the so called Emergency Use Authorizations. This meant that the safety performances, usually garnered over an extended amount of time, were not obtainable at the time that the MnSCU was in the process of deploying the various technologies. Second, given the volume of vaccines and therapeutics that were deployed since the start of vaccination campaigns, and the efficacy of these campaigns in terms of the number of doses administered in the short span of time globally, there was increased need for data gathering mechanisms or surveillance systems to detect possible AE. Thirdly, exposure of the diverse and global population including the elderly patients, pregnant women, patients with co-morbid conditions prompted the need to have post-marketing surveillance to capture variations in responses. Fourthly, the spread of misperception and concerns about the side effects contributed to the scepticism regarding vaccines, which egalised the importance of communication of pharmacovigilance results to the public. Fifthly, there was a constant change and evolution of new viral variants that affected the effectiveness and safety of vaccines as well as a therapeutic treatment option and this required constant review and redesign of the

monitoring procedures. Finally, many healthcare systems encountered challenges in effectively collecting and analyzing safety data, stemming from issues like underreporting, a lack of standardization, and resource constraints [16-19].

2. DRUG SAFETY MONITORING FRAMEWORKS

2.1 Overview of Pharmacovigilance

Pharmacovigilance (PV) is the scientific and operational processes related to the detection, evaluation, understanding, and prevention of adverse effects or any drug-related problem. Pharmacovigilance is an essential requirement for the safety and efficacy of pharmaceutical products, especially in the fast-track development of therapeutics and vaccines for emerging infections like COVID-19. The basic objectives of pharmacovigilance are the detection of previously unknown adverse drug reactions (ADRs), improvement of patient care and safety, and affirmation of the benefits of drugs compared to the risks. The basic principles of pharmacovigilance are proactive action for drug safety, e.g., spontaneous reporting systems, signal detection, risk assessment, and regulatory action. These are complemented by national and international regulatory bodies, e.g., the World Health Organization (WHO), the U.S. Food and Drug Administration (FDA), and the European Medicines Agency (EMA), that provide guidelines and regulations for the collection and evaluation of safety data [20].

Pre-Marketing and Post-Marketing Surveillance

Pharmacovigilance comes in two major stages: pre-marketing and post-marketing surveillance. The two stages are crucial in the evaluation of the safety of medications and the protection of patient health.

Pre-Marketing Surveillance

Pre-marketing surveillance includes safety assessments conducted during clinical trials before a drug or vaccine is approved for public consumption. This process includes:

• Preclinical Studies: Animal and laboratory studies determine the first safety profile and pharmacokinetics of a compound [21].

Clinical Trial Phases:

Phase I: Uses a small number of healthy volunteers to ascertain safety, dosage, and pharmacokinetics.

Phase II: Larger patient population to ascertain efficacy and carry out further safety trials.

Phase III: Carrying out large-scale trials in thousands of individuals to establish the drug's effectiveness, keep track of possible side effects, and compare its efficacy with current treatments. Clinical trials are not without their natural limitations. The trials are carried out in artificial settings with a limited population, which cannot possibly reflect the occurrence of infrequent or prolonged side effects. The limitations make post-marketing surveillance [22] necessary.

Post-marketing surveillance

After approval and release of the drug or vaccine in the market, ongoing surveillance is necessary to detect any adverse effects or safety issues not already known. This covers:

• **Spontaneous Reporting Systems (SRS):** There is patient and hospital manager reporting of ADRs to agencies like the FDA's Vaccine Adverse Event Reporting System (VAERS) and WHO's VigiBase [23].

• **Active Surveillance Programs:** These include active data collection methods such as electronic health records (EHR) review and cohort studies to assess real-world safety outcomes.

•**Phase IV Clinical Trials:** Studies conducted after drug marketing to further assess long-term safety and efficacy.

• **Risk Management Plans (RMPs):** The regulatory agencies require manufacturers to develop RMPs that outline how potential risks are to be managed and mitigated. The COVID-19 pandemic highlighted the necessity of robust pharmacovigilance systems since vaccines and treatments were developed and approved under emergency use authorizations. Large-scale monitoring programs, as demonstrated by the global cooperation of regulatory agencies and real-world evidence studies, have provided vital information on vaccine safety and management of adverse events [24].

2.2 Regulatory Guidelines for Monitoring Drug Safety

WHO Guidelines

The World Health Organization (WHO) has played an important role in developing global guidelines for monitoring drug safety, especially in the context of the COVID-19 pandemic. WHO guidelines stress a systematic approach to pharmacovigilance that enables timely detection, assessment, and prevention of COVID-19 treatment and vaccine-related adverse

drug reactions (ADRs). WHO has taken measures like real-time safety monitoring, international collaboration among countries, and building reporting systems to monitor vaccine safety in real-world practice. WHO's Global Advisory Committee on Vaccine Safety (GACVS) has played a significant role in reviewing safety data from countries. GACVS recommends advice based on continuous monitoring of adverse events following immunization (AEFI). WHO also assists low- and middle-income countries (LMICs) in strengthening their pharmacovigilance systems through technical support and training programs. Another important component of WHO's safety monitoring guidelines is the utilization of digital tools like VigiBase, which compiles and analyzes safety reports from national regulatory authorities. The database enables the detection of rare but serious adverse events that were not identifiable during clinical trials. The guidelines also stress the need for risk communication with the public in order to ensure confidence in vaccines and therapeutic interventions [25].

FDA, EMA, and CDSCO Frameworks for COVID-19 Drugs and Vaccines

United States Food and Drug Administration (FDA)

The Food and Drug Administration (FDA) has embarked on an aggressive approach to monitoring COVID-19 treatments and vaccines. FDA pharmacovigilance policies entail pre- and post-marketing surveillance, rigorous adverse event reporting, and review of real-world data. One of the principal regulatory tools employed by the FDA is the Risk Evaluation and Mitigation Strategy (REMS), a system aimed at ensuring benefits of a drug exceed risks. Vaccine Adverse Event Reporting System (VAERS), co-managed by the FDA and the Centers for Disease Control and Prevention (CDC), is a cornerstone of vaccine safety monitoring. Through VAERS, healthcare providers and the public can report suspect adverse effects, enabling the FDA to respond immediately if necessary. The Sentinel Initiative, another cornerstone of the FDA's monitoring strength, leverages electronic health records and claims data to assess vaccine safety at scale. The FDA has, in addition, mandated that pharmaceutical firms conduct post-marketing trials and Phase IV clinical trials to gather data on long-term safety. Emergency Use Authorizations (EUAs) granted to COVID-19 vaccines and treatments were accompanied by strict conditions for continuous monitoring and regular reporting of safety [26].

European Medicines Agency (EMA)

The EMA has a strong system for monitoring the safety of medicines and vaccines through its EudraVigilance system. The system facilitates the collection and analysis of suspected adverse

drug reactions by member states in the European Union. The Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA is tasked with reviewing these reports and providing safety advice. One of the biggest efforts by the EMA in the context of the COVID-19 pandemic was the creation of the COVID-19 Task Force, which collaborated closely with manufacturers to review safety data in real time. The agency also implemented increased transparency practices, releasing routine safety information on COVID-19 vaccines and medicines through publicly available reports. The conditional marketing authorization (CMA) pathway of the EMA enabled the rapid approval of COVID-19 vaccines without compromising on safety standards. This allowed for any new issues of safety emerging to be addressed promptly through regulatory measures such as change in labeling, restriction of use, or withdrawal of authorization if needed [27].

Central Drugs Standard Control Organization (CDSCO) - India

The CDSCO, as an organization under India's Ministry of Health and Family Welfare, regulates drug safety monitoring under the Pharmacovigilience Programme of India (PvPI). It is an Indian Pharmacopoeia Commission (IPC) program that ensures systematic collection and evaluation of adverse event reports on COVID-19 vaccines and therapeutics. CDSCO enforced stringent post-marketing surveillance for vaccines such as Covaxin and Covishield during the pandemic. Adverse events following immunization (AEFI) were monitored closely, and comprehensive safety reports were submitted to regulatory authorities. The CDSCO also coordinated with international regulatory authorities, such as the WHO and EMA, to harmonize safety monitoring activities with global standards.The Indian government also initiated programs such as the CoWIN platform, which not only enabled tracking of vaccinations but also acted as a platform for real-time monitoring of adverse events. The regulatory authority also required pharmaceutical companies to submit risk management plans (RMPs) and periodic safety update reports (PSURs) to ensure ongoing safety monitoring [28].

2.3 Spontaneous Reporting Systems (SRS) and Signal Detection

Function of the WHO VigiBase, VAERS, EudraVigilance

Spontaneous reporting systems (SRS) are critical to post-marketing surveillance of therapeutics and COVID-19 vaccines. SRS facilitates adverse drug reaction (ADR) and vaccine adverse event reporting by healthcare professionals, patients, and pharmaceutical companies. The primary role of SRS is to detect safety signals of underappreciated risks with medical products. The World Health Organization (WHO) VigiBase, which is operated by the Uppsala

Monitoring Centre (UMC), is the largest worldwide database of individual case safety reports (ICSRs). VigiBase collects reports from over 170 countries that are part of the WHO Programme for International Drug Monitoring (PIDM). It uses advanced statistical algorithms, such as the Bayesian Confidence Propagation Neural Network (BCPNN), to identify disproportionate reporting signal detectability (DSig). VigiBase was instrumental in revealing underappreciated adverse events due to COVID-19 vaccines, such as myocarditis and thrombosis with thrombocytopenia syndrome (TTS) due to adenoviral vector vaccines [29]. The Vaccine Adverse Event Reporting System (VAERS) is an American passive surveillance system co-operated by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA). VAERS facilitates healthcare professionals and the general public to report after-immunization adverse events (AEFI). Though it is not utilized for the determination of causal relationships, it provides an early signal for potential safety concerns. During the COVID-19 pandemic, VAERS was found to be accountable for identifying the increase in incidence of anaphylaxis after the administration of mRNA vaccines, which led to changes in safety guidelines [30].

EudraVigilance, the European Union pharmacovigilance database governed by the European Medicines Agency (EMA), is an integral part of the worldwide Signal Reporting System (SRS) network's core component. The database gathers and analyzes reports on suspected adverse drug reaction to medicinal products, including vaccines and COVID-19 drugs. EudraVigilance uses data-mining techniques in conjunction with signal detection techniques to track the benefit-risk profiles of medicinal products. Its utility was demonstrated in the evaluation of thromboembolic risk with AstraZeneca's ChAdOx1-S (Vaxzevria) vaccine, resulting in focused regulatory measures [31].

Challenges of Underreporting and Bias

However, inherent in every SR system is some limitations majorly due to under reporting and skewed reporting. The paper concludes that only about 30% of adverse events are reported to SRS databases thus under representation of the actual portfolio of safety of medical products. Lack of awareness and training among the healthcare staff, lack of time to complete the forms, concern for legal issues, and voluntary nature of such systems also influence the under-reporting factor.Alsor, the issue of biased report leads to questionable signal detection. AEFI reports may be affected by experiences mediated through the mass media, popular view of AEFI, and actions by a regulatory agency. For example, raising awareness on rare thrombotic

occurrence to the adenoviral vector vaccines increased the reporting rate, thus inflating the risk numbers. Along these lines, recall bias threatens the quality of reported data especially when the patient remembers and necessarily links symptoms with vaccination.To manage all these, regulatory agencies have come up with active surveillance systems, automated data mining, and cross checking of EHRs with SRS databases.The integration of artificial intelligence (AI) in pharmacovigilance, coupled with real-world evidence (RWE), is enhancing the detection and analysis of safety signals. Furthermore, efforts to improve healthcare professional and public engagement through education and streamlined reporting processes have been encouraged to enhance data completeness and quality [32].

2.4 Active Surveillance and Real-World Evidence (RWE)

Monitoring of COVID-19 therapeutics and vaccines' efficacy and safety is possible due to the Active surveillance and Real-World Evidence methodologies. The problems with using clinical trials as the gold standard have been Summer anticipated due to restrictions of environment and time span of the clinical trial follow up. Active surveillance makes use of real-time safety information from factors such as digital health, EHRs and other sentinel surveillance networks to inform regulatory decisions.

Digital Health Technologies (AI, Big Data Analytics)

The advancements in technology like the use of AI and big data in monitoring the safety of drugs have emerged to be efficient ways of analyzing large amount of data in real time than the conventional methods. These include artificial intelligence and machine learning models that can recognize patterns of ADR and other related events with vaccines. These systems also include information collected from social media, health monitoring devices, and patient self-reports that allow safety signals that may not appear in standard reporting systems to be identified [33].Big data analytics also enable synthesis of information coming from clinical trials, hospital records, PV databases, and post-marketing studies. The aspect of big data processing helps the regulatory agencies like USA's FDA and EMA to make quick safety evaluations in real-time addressing emerging safety issues Similarly, the natural language processing (NLP) helps in the enhancement of safety monitoring from unstructured sources like science publications and reported incidences. This helps in monitoring and documenting rehabilitative adverse events which may not be distinguished during clinical trials [34].

Role of Electronic Health Records (EHR) and Sentinel Surveillance

EHRs are useful for ADaM activities as they are wide, reliable and structured sources of patients' data. EHR also permits continuous monitoring of those vaccinated or provided with COVID-19 therapeutical aid for any delayed or delayed adverse effects. The linking of EHRs with pharmacovigilance databases automates adverse event reporting making it easier on the side of health care providers besides enhancing on accuracy. Sentinel surveillance networks are another layer of monitoring since they are data gathering and analyzing systems that obtain information from selected sentinel sites. Some examples include FDA's Sentinel Initiative as well as the European Union's EudraVigilance system rely on distributed data networks for post-market safety evaluations. These networks are designed with query programs that subsequently monitor specific signals in real-world settings for COVID-19 treatments and vaccines. Additionally, utilizing EHRs to link them with immunization registries, gives more information on vaccine efficacy and safety of the population, particularly in subpopulations like immunocompromised persons and pregnant women. Information exchange and aggregation of data enable decision-making and guide public health policies on the appropriate way of approaching COVID-19 vaccination [35].

3. SAFETY MONITORING OF COVID-19 THERAPEUTICS

3.1 Overview of COVID-19 Therapeutics

COVID-19 had an unforeseen impact throughout the world and resulted in a steep upsurge in terms of the production and confirmation of therapeutic agents. Different management approaches such as antiviral agents, monoclonal antibodies, and immunomodulators were used in managing the infection and its related complications. Nevertheless, there was a rising need for close monitoring of these therapeutics due to the fast pace of development. This part of the literature review assesses the efficacy of important COVID-19 medicines and the method of risk supervision.

3.1.1 Antivirals

Remdesivir

Remdesivir, an adenosine nucleotide analog, was one of the first antiviral drugs granted emergency use authorization (EUA) for the treatment of COVID-19. It inhibits the viral RNA-dependent RNA polymerase, thereby reducing viral replication . Clinical trials demonstrated its ability to shorten recovery time in hospitalized patients with moderate to severe COVID-

19.However, side effects relating to safety include hepatotoxicity, nephrotoxicity, as well as infusion-related hypersensitivity reaction. Most of these side effects have been reported during post-marketing surveys and other surveillance, and include the aggravation of liver enzyme elevation and acute kidney injury, especially in patients with underlying liver or kidney diseases [36].

Molnupiravir

Molnupiravir was designed to be an orally bioavailable prodrug aimed at causing lethal mutagenesis in the SARS-CoV-2 virus. It was authorised for the EUA for non-severe COVID-19 for patients who are vulnerable to develop severe illness. However, this description gave rise to mutagenic effects and teratogenicity that placed limitations on pregnant people and continued to monitor for genotoxic effects. Moreover, observation from post-marketing analysis of the drug revealed that it has gastro-intestinal side effects and some interactions with other drugs [37].

Paxlovid (Nirmatrelvir-Ritonavir)

Paxlovid, incorporating nirmatrelvir which is an SARS-CoV-2 protease inhibitor and ritonavir, a CYP3A inhibitor has shown promising results on cutting hospitalization and mortality in high-risk patients. However, monitoring of adverse effects identified drug-drug interactions because of the ritonavir's ability to inhibit CYP3A, particularly when the patients on polypharmacy. Other side effects include altered taste sensation, diarrhoea and hepatotoxic effects, for which further post marketing surveillance were deemed necessary in the long-term [38].

3.1.2 Monoclonal Antibodies

Casirivimab-Imdevimab

Fedinghina, Another neutralizing synthetic monoclonal antibody with an active ingredient in casirivimab-imdevimab, a mixture of two different monoclonal antibodies that target the spike protein of SARS-CoV-2, is available for outpatient treatment of mild to moderate COVID-19 in high risk individuals. It has also been noted that clinical trials have led to decrease in viral load as well as hospitalizations . However, the new variants such as the omicron variant have some level of resistance to this therapy and therefore the use reduced. Mentioned safety issues are hypersensitivity reactions, anaphylactic reactions, and infusion reactions and hence, require the real-time pharmacovigilance intention [39].

Sotrovimab

Sotrovimab, another monoclonal antibody therapy targeting the spike protein was effective on some of the SARS-CoV-2 variants. Its major application was in home care of the high risk patients to avoid exacerbation of the disease status. Safety data revealed a favorable picture though few reports of hypersensitivity reactions as well as infusion reaction related adverse effects were reported for the need of further safety monitoring. Furthermore, development of resistance mutations has become a concern on the long-term effectiveness of the drug [40].

3.1.3 Immunomodulators

Dexamethasone

Dexamethasone, a corticosteroid drug, has been administered to tackle inflated inflammation and cytokine storm in critical COVID-19 patients. RECOVERY also established its ability in reducing mortality in a ventilated and oxygen-dependent population. Some of the issues with the use of corticosteroids were septicemia, hyperglycemia, adrenal suppression, especially where the over administration of the corticosteroids was concerned. That is why post-marketing studies underlined the necessity of cautious observation of immunocompromised patient taking corticosteroid therapy [41].

Tocilizumab

Springing from this study, Tocilizumab, IL-6 receptor antagonist, received approval for the emergency use in treating severe COVID-19 with systemic inflammation. Randomised trials also indicated that critically ill patients benefited from the use of human" We are aware that several clinical trials have established that critically ill patients benefited from the use of human. However, as was shown in reports on pharmacovigilance, the possibilities of an increased risk of opportunistic infections, neutropenia, and liver dysfunction, therefore, the necessity for further regularly monitoring the laboratory indicators during the therapy was ascertained [42].

Baricitinib

Baricitinib is an antirheumatic drug, which is a Janus kinase (JAK) inhibitor, and was chosen for COVID-19 treatment based on its anti-inflammatory effect. It was superior and provided evidence of improvement in the mortality and use of mechanical ventilation. But safety

concerns high with thromboembolism, hepatic dysfunction, and reactivation of latent infections for groups at risk thus they needed to be monitored closely [43].

3.2 Common Adverse Drug Reactions (ADRs) Reported

Organ-Specific Toxicities (Liver, Kidney, Cardiovascular Effects)

COVID-19 therapies have been reported to be related to severities of organ toxicity including hepatic, nephrotoxicity, and cardiovascular damage. Liver injury has been also reported as a rather significant issue, including the cases with remdesivir and tocilizumab leading to increased levels of hepatic enzymes and, in some instances, acute liver damage. Likewise for nephrotoxicity, where several studies have indicated AKI in hospitalized patients administered with antiviral drug namely remdesivir. Cardiovascular toxicities have also been of great concern in these drugs and medicines that cause cardiovascular diseases are likely to impact its use. It is really known that a combination of HCQ and azithromycin brings a tendency to increase QT interval, which leads to the dangerous condition with increased risk of arrhythmia and sudden cardiac death. Similarly, orala, the corticosteroids utilized for further worsening the condition by causing hypertension and thromboembolic events in severe COVID-19 patients and to manage the same, which has added on more difficulty in patient care [44].

Drug-Drug Interactions

Like other drugs, DDIs presented concerns during the pandemic due to possible use of multiple medications at once together with COVID-19 therapeutics. For a instance, Ritonavir-boosted nirmatrelvir (Paxlovid) has developed a reputation of significantly inhibiting cytochrome P450 enzymes making it interact with anticoagulants, immunosuppressants and statins. Another of the problems encountered was the interference between antiviral agents and corticosteroids. It therefore appeared that when dexamethasone was given together with remdesivir, the drugs' pharmacokinetics were changed in a way that might diminish the effectiveness of either drug. Likewise, when applying immunomatology like tocilizumab in combination with JAK inhibitors, there were some perspectives that included serious issues such as immunosuppressive activity and predisposition to opportunistic infections were also reported [45].

3.3 Post-Marketing Safety Surveillance Findings

Case Studies of Safety Alerts and Drug Withdrawals

Monitoring of safety after the drug was marketed was very important in establishing other side effects which had not been observed during the clinical investigation. The first safety alert that was commonly reported was hydroxychloroquine. For example, HCQ was approved under the Emergency Use Authorization (EUA) and was pulled due to large clinical trials that showed an increase in mortality rate, heart-related complications without showing potential in treating COVID-19.In the same way, Johnson & Johnson COVID-19 vaccine being temporarily halted because some patients reported TTS. Another side effect was the COVID-19 Vaccine which arose from blood clots and low platelet count Recently, molnupiravir, an oral antiviral, has been concerning regarding its mutagenic property. Its use was later approved for emergency, and while investigations are still being conducted about the drug's impact in the long term, especially in pregnant women with other immunocompromised individuals [46].

Challenges in Identifying Long-Term Effects

A major problem that exists in post-marketing surveillance is understanding the late onset symptoms of COVID-19 treatments. Because of the increase in the use of many drugs and vaccines in the recent past given their approval for emergency use, there is limited reliable, long-term data that support the drugs and vaccines' safety. For example, there are some issues have been raised regarding the side effects such as myocarditis and pericarditis observed in vaccine developed by Pfizer-BioNTech and Moderna especially in young male although majority of the cases have been mild and self-administered. Another one is conflict of interest and an extremely low reporting of adverse drug reactions (ADRs). Some systems of identifying safety signals depends on passive reporting system which include only the VAERS in United States and this may cause biases and incomplete data. Also, it is challenging to differentiate between allergic or side effects of the vaccines and the post-vaccine complications of long Covid [47].

4. SAFETY MONITORING OF COVID-19 VACCINES

4.1 Overview of COVID-19 Vaccines

4.1.1 mRNA Vaccines (Pfizer-BioNTech, Moderna)

The COVID-19 vaccines that use mRNA as their agents of operation have proved to be the biggest innovation in vaccinology as witnessed in the current pandemic. BNT162b2 Pfizer BioNTech and mRNA 1273 Moderna were the first two vaccines that received Emergency Use Authorization from approving bodies like Food and Drug Administration and the European Medicines Agency among others. These vaccines use lipid-based nanoparticles containing mRNA that has the genetic sequence coding for the spike (S) protein of SARS-CoV-2 upon injection and the body's immune response is initiated.The safety of mRNA vaccines has been previously demonstrated through phase III efficacy trials and post-launch surveillance. The common side effects include pain at the injection site, tiredness, headache, muscle pain, and mild fever also subsides within 1-2 days. However, there are minor side effects like myocarditis and pericarditis majorly in young males after the second dose. Such findings have resulted to ongoing evaluation of the risks and benefits by the health departments [48].

4.1.2 Vector-Based Vaccines (AstraZeneca, Johnson & Johnson, Sputnik V)

There is a type of vaccines called vector-based that is the AstraZeneca ChAdOx1 nCoV-19 (Vaxzevria), Johnson & Johnson Ad26.COV2.S(Janssen), Sputnik V, among others, that use a virus to deliver genetic material encoding SARS-CoV-2 spike protein. These vaccines have led to immune responses and have been used for global immunization purposes.Vector-borne vaccines have been probed to be linked to adverse effects, though they are severe and rare. VITT has recently been identified as one of the rare adverse effects after COVID vaccination specifically AstraZeneca and Johnson & Johnson vaccines. The symptoms of VITT include thrombosis of the atypical site such as cerebral venous sinuses and low platelet levels In This regard, it needs constant monitoring and requires effective treatment.The Sputnik V vaccine has been developed by the Gamaleya Research Institute and uses two different vectors p Ad26 and pAd5 in a heterologous prime boost strategy. In terms of post-market safety, Sputnik V has received relatively low reporting from certain regions owing to which its safety profile and efficacy in preventing severe COVID-19 have been understood to be high [49].

4.1.3 Inactivated Vaccines (Covaxin, Sinopharm, Sinovac)

Covaxin (Bharat Biotech), Sinopharm, and Sinovac are some of the inactivated vaccines that use virus particles which are rendered useless through the process of inactivation but are intact in form. These vaccines received have been administered especially in most of the LMICs and this has been mainly Sanford guide. Safety reports data show that inactivated vaccines are safe with mild to moderate side effects that include pain at the site of injection, malaise, and low-grade temperature. Malaise and anaphylactic reactions are not frequent. However, controversy has been recorded concerning the variability of these prevention measures in dealing with new strains of the SARS-CoV-2 virus. Ultimately, the long-term follow up of these vaccine remains through pharmacovigilance activities and real life studies to establish any safety concerns that may arise [50].

4.2 Vaccine Pharmacovigilance Strategies

4.2.1 Pre-licensure Clinical Trials and Limitations

Phase III clinical trials are/can be also important in the assessment of COVID-19 vaccines adren their efficacy and safety before they are released onto the market. These are three, Phase I in which a first few volunteers with no disease are given the vaccine to test their immune reaction, Phase II where hundreds of individuals are given the vaccine to determine the dosage that should be used and any side effects that may be observed, and Phase III that involves thousands of the population to confirm that the vaccine works and if there are any effects that are rare to be observed. But it would be foolish to ignore these three trials altogether, as they really do yield important data on such matters. This pandemic drew scant attention to the shortening of the clinical trial period hence reducing the time taken to conduct long term safety tests on the vaccines. Also, any sample of clinical study might not reflect population characteristics in certain aspects, including pregnant patients, the elderly, and other populations with other conditions [51].

4.2.2 Post-Marketing Surveillance (VAERS, EudraVigilance)

As with any drugs and vaccines, post-marketing surveillance systems steps in to identify the adverse effects that are not detected in the course of clinical trials of vaccines that get the green light by the regulatory authorities. The Vaccine Adverse Event Reporting System (VAERS) in United States and Eudra Vigilance in EU present the data of all alleged adverse effects of vaccines which can be reported by physicians, manufacturers and the public. These systems

assist in identifying safety alerts in a bid to conduct further investigation with a view of taking necessary regulatory measures. For example, the information related to some rare adverse effects includes myocarditis in young males and thrombosis with thrombocytopenia syndrome subsequent to receiving vaccines developed from mRNA COVID-19 or those developed from adenoviral vectors, respectively. However, the VAERS and EudraVigilance are passive reporting system and any adverse reporting usually depends on the cases reported meaning that relevant information could be missing. The active surveillance studies like CDC's Vaccine Safety Datalink (VSD) and ongoing with EMA also have the same advantages being done through data collected from electronic health records and registries and have certain limitations [52].

4.3 Adverse Events Following Immunization (AEFIs)

4.3.1 Common Side Effects

It is worth noting that most of the available COVID-19 vaccines have some mostly moderate and rare side effects which are regarded as immune response. Some of the side effects reported are fever, fatigue, headache, muscle aches, and pain at the site of injection. Such reactions are common as the body develops an immune response to the vaccine and usually last for a few days only. These side effects were also revealed to be more prevalent after the second dosing of the mRNA vaccines, and were more common among young persons as they have more vigorous immune reactions [53].

4.3.2 Severe AEFIs

Contrary to the common mild side effects, some serious adverse effects have also been observed after COVID-19 vaccination. One of the most important adverse was myocarditis and pericarditis, mainly reported in young males after mRNA vaccines, Pfizer-BioNTech, BNT162b2 and Moderna, mRNA-1273. These conditions were mild and require medical attention for treatment in most of these cases. The next life-threatening complication that was associated with adenoviral vector vaccines particularly the AstraZeneca's Vaxzevria and Johnson & Johnson's Janssen vaccines was Thrombosis with Thrombocytopenia Syndrome. TTS is basically a medical condition associated with the presence of clots along with reduced platelet count in the blood and calls for urgent treatment. There are however other side effects side effects which include Anaphylaxis, although this was a rare condition which occurred between 2 to 5 cases per one million doses. Such recommendations posed certain new

recommendations of vaccines like age specific guidelines and other appropriate vaccines suggested for patients who are likely to develop higher AEFIs [54].

4.3.3 Special Population Concerns

Those individuals such as pregnant women, older persons or persons with compromised immune systems were required to have additional safety supervision. Due to the fact that early cases of the vaccines being administered were done under Phase III trials most pregnant women were not vaccinated and thus there is no conclusive evidence whether the vaccines are safe for such individuals. Subsequent observational studies and real-world data also revealed that mRNA COVID-19 vaccines were not dangerous in pregnancy and offered protection to both the mother and the fetus without complications affecting the pregnancy outcome. The closer contacts to the elderly were also greatly affected since the elderly are more vulnerable to severe outcomes of COVID-19. Early vaccine effectiveness exceptions based on the immune compromise that people face as they age were proven to offer adequate protection against the severe disease and hospitalization as analyzed in observational studies. The study also showed the immune response to the vaccine heterogeneity in immunocompromised patients, for instance, cancer treatment or transplant recipients. To strengthen the immune response and minimize breakthrough infections, booster shot and other preventive measures were advocated for them [55].

4.4 Long-Term Safety Considerations

Monitoring Booster Doses and Variant-Specific Vaccines

For this reason, booster doses and variant-specific COVID-19 vaccines have been successfully implemented and administered to help sustain immunity against new emerging strains of SARS-CoV-2. Initial pickup studies and EUA were conducted on the sense of short-term safety, and efficacy, while there is the need to assess longer-term impacts that may be associated with repeated immunizations, as for safety. Pharmacovigilance databases such as VAERS and EudraVigilance have been useful in monitoring booster adverse effects following immunization. According to previous analyses, booster doses do not deviate much from the established courses of potential adverse effects, but there are certain categories of patients with chronic conditions, which may be specified as potentially susceptible to myocarditis and pericarditis, especially young males, who have been adversely affected by the mRNA kinds of vaccines.

Due to this, variant specific vaccines for instance the Omicron adjuvanted vaccines have also been thoroughly evaluated in terms of safety and immunologic effectiveness. Because of this the patients need to be closely monitored both in terms of the short term effects involving immune imprinting where immunity produced to a particular vaccine may have an impact on the production of immunity against subsequent vaccines with antigenically similar strains of the virus. With the further development of booster strategies, the effectiveness of those strategies should be based on empirical data to effectively determine durations between booster doses and components that would give long-lasting immunological protection with a low risk of adverse reactions [56].

Potential Long-Term Autoimmune and Inflammatory Risks

As with most new therapeutic interventions, concerns with respect to long-term autoimmune and inflammatory effects of the COVID-19 vaccines remained a valuable topic of post-marketing surveillance. Though such autoimmune-related large scaled RCTs as well as real-world data have not demonstrated highly relevant severe autoimmune reactions, there have been sporadic reports of immune-mediated adverse effects of vaccination. Complications of autoimmune reactions including Vaccine-induced Immune Thrombotic Thrombocytopenia related to adenoviral vector based vaccines and myocarditis in relation to the mRNA vaccines have been reported. These reactions are metabolic and immunologic reactions, which involve molecular mimicry, in which the vaccines may cause antibodies to form against tissues in the body. Also, further research has been done on inflammation, reactions after several immunisations with or without preexisting heritable sub-phenotypes.Also, post-vaccination inflammation symptoms together with genomics have continued to be under research; Long COVID-like vaccine symptoms. Although most vaccine recipients may suffer minor adverse effects, research into the association of vaccination and the long-term autoimmune and inflammatory disorders persists.There are also large scale cohort studies, EHR based analysis, and patient reported outcome assessments in pharmacovigilance to observe and address possible risks. As for the future studies, efforts should be made on optimizing the vaccine formulations and the mode of adjuvants that can boost immunogenicity without causing unwanted immune stimulation [57].

5. LESSONS LEARNED FROM COVID-19 DRUG SAFETY MONITORING

5.1 Strengths of the COVID-19 Safety Monitoring Approach

Speed of Vaccine Development vs. Robust Safety Evaluation

Emergency use authorization (EUA) went to multiple COVID-19 vaccines following an unprecedentedly short period of one year since the pandemic began. The development process reached its high speed through concurrent clinical trials combined with fast regulatory decisions and major funding from both government institutions and private organizations. The rapid development timetable got support through successful implementation of extensive clinical trials combined with systematic post-marketing surveillance. To minimize security risks regulatory agencies like the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) enforced recurring checks during development while requiring pharmaceutical corporations to document all unfavorable incidents [58].

Global Collaboration in Pharmacovigilance

Major drug safety monitoring during COVID-19 period succeeded because regulatory agencies together with research institutions and pharmaceutical companies formed wide-ranging global collaborations. Through its programs and mission the World Health Organization (WHO) together with Coalition for Epidemic Preparedness Innovations (CEPI) provided essential coordination for safety surveillance within various geographic regions. Through real-time pharmacovigilance networks that linked global data sharing the identification and resolution of safety issues became prompt which validated the need for future international pandemic cooperation [59].

5.2 Challenges and Limitations

Rapid Rollout and Real-Time Monitoring Difficulties

The quick vaccine launch during the pandemic brought new obstacles to near-time monitoring operations. Old post-market surveillance systems were unable to process the extensive data volumes sufficiently to detect or analyze uncommon adverse events effectively. The Vaccine Adverse Event Reporting System (VAERS) in the United States along with other spontaneous reporting systems face limitations because scientists find it challenging to accurately measure both underreporting incidents and data inconsistencies [60].

Public Skepticism and Misinformation

The effective tracking of drug safety developed key challenges because of incorrect information and negative public attitudes toward the process. The spread of incorrect vaccine side effect information by social media users caused a decrease in public trust toward health authorities and vaccine hesitancy throughout society. Both public information initiatives and transparent vaccine data sharing and leadership involvement from community members were introduced to fight misinformation about vaccine safety. Practice of vaccine hesitancy continued to exist in various regions despite these newly implemented strategies which demonstrates that better communication methods for risk assessment need development for future public health situations [61].

5.3 Ethical Considerations

Balancing Rapid Approval vs. Long-Term Safety

The urgent need to expedite vaccine approvals created an ethics problem because it led to potential safety issues that researchers needed to address during the COVID-19 pandemic. Emergency authorizations forced medical professionals to carry out expedited clinical trials that resulted in fewer long-term follow-up studies at the time vaccines reached public markets. Monitoring programs of real-world evidence operated after approval yet authorities remained alert for any enduring adverse effects that drove them to modify their regulatory approaches. The fundamental framework of both public trust preservation and responsible choices depended on preventive approaches linked with perpetual safety checks [62].

Informed Consent and Transparency in Data Sharing

Prior to implementing data collection practices it was essential to obtain patient consent and maintain full transparency about information sharing to resolve ethical challenges in COVID-19 treatments and vaccines. Clinical trial participants needed to get full information regarding potential risks and benefits by mandate from regulatory agencies before they could join trials. The open-access safety databases together with peer-reviewed publications enabled independent researchers to verify safety data and validate scientific findings through their scrutiny process. Sanofi Pasteur put several measures in place to strengthen ethical standards as well as scientific integrity through the vaccination process while boosting public trust [63].

6. FUTURE DIRECTIONS AND RECOMMENDATIONS

6.1 Improving Global Pharmacovigilance Systems

Strengthening Real-World Evidence Collection

The COVID-19 pandemic highlighted the need for strong real-world evidence (RWE) to validate clinical trial information. Conventional randomized controlled trials (RCTs) provide ample data on drug safety but lack information on long-term adverse effects and subset population effects. Real-world data (RWD) need to be collected systematically in comorbid and heterogenic populations to enhance pharmacovigilance. Electronic health record (EHR) integration, patient registries, and post-marketing surveillance reports can widen the safety surveillance scope. Data collection in multiple healthcare settings and nations helps researchers detect long-term and rare side effects that may not be detectable in clinical trials [64].

Standardizing International Reporting Mechanisms

One of the key issues faced during the COVID-19 outbreak was the lack of a harmonized system of pharmacovigilance. Different countries had different standards of reporting adverse drug reactions (ADRs) and vaccine-related adverse events, and this led to disparity in interpreting safety information. Harmonization of worldwide pharmacovigilance systems is important to enable collective safety evaluation. Bodies like the World Health Organization (WHO) and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) should lay down identical guidance on ADR reporting. Creation of a centrally archived, worldwide accessible database can enable real-time sharing of information and improve the timeliness of safety warnings [65].

6.2 Role of Digital Technologies in Drug Safety

AI-Based Signal Detection and Predictive Analysis

Artificial intelligence (AI) is currently a game-changer in pharmacovigilance. AI algorithms are capable of sifting through huge volumes of data to identify early warning signs of possible adverse effects of COVID-19 therapeutics and vaccines. Machine learning algorithms are able to recognize patterns from patient reports, social media, and medical literature to generate real-time pharmacovigilance intelligence. Predictive analytics can enable regulatory agencies and healthcare professionals to forecast and prevent safety concerns prior to adverse events

occurring on a large scale. AI-enabled systems like the FDA's Sentinel Initiative and the European Medicines Agency's (EMA) EudraVigilance have proven that AI can be applied to enhance drug safety monitoring [66].

Blockchain for Transparent Sharing of Pharmacovigilance Data

The use of blockchain technology in pharmacovigilance will address data transparency, security, and interoperability concerns. A tamper-proof and decentralized record of the ADR report can be achieved with the use of blockchain such that all stakeholders, including regulators, healthcare professionals, and patients, can be offered accessible, verifiable data. It will be able to automate reporting through the use of smart contracts such that it can eliminate the threats of under-reporting and data manipulation. Through the real-time and tamper-evident transfer of information, blockchain can improve global confidence in pharmacovigilance systems and deliver an injection of credibility to COVID-19 drugs and vaccine-related safety data [67].

6.3 Policy Recommendations for Future Pandemics

Flexible Regulatory Frameworks for Emergency Use

The rapid development and deployment of COVID-19 vaccines and treatments highlighted the need for more flexible regulatory approaches during public health emergencies. Standard approval processes can be time-consuming, potentially delaying access to life-saving medicines. Flexible regulatory approaches such as rolling reviews and conditional marketing authorizations must be formalized to bring vaccines and medicines to market faster during pandemics. Organizations such as the FDA, EMA, and WHO must work together to develop pre-pandemic preparedness plans so that EUAs are based on thorough but accelerated assessments of safety and efficacy [68].

Improving Risk Communication Strategies

Risk communication needs to be used to increase public confidence in vaccines and therapeutics. The COVID-19 pandemic brought to the fore undue misinformation and vaccine hesitancy, and hence the demand for transparent and evidence-based risk communication approaches. Governments and health authorities need to create uniform risk communication frameworks that have anticipatory public engagement as a priority. Multilingual engagement, open communication, and collaboration with social media to counter misinformation can augment public confidence. Patient-centered communication approaches, such as direct

patient-physician communication and community outreach programs, can reduce anxiety regarding vaccine safety [69].

CONCLUSION

The COVID-19 pandemic was a historic global health crisis that required the rapid development and release of therapeutics and vaccines. While these activities were crucial in reducing the disease burden, they also highlighted the imperative for strong pharmacovigilance systems to secure safety and efficacy. The convergence of pre-marketing and post-marketing surveillance systems was at the center of the identification and control of adverse drug effects, highlighting the value of real-time surveillance and adaptive regulatory systems. The main lessons from drug safety monitoring during the COVID-19 pandemic are the absolute need for real-time surveillance with digital health technologies, the requirement for open communication with the public to counter misinformation, and the value of global cooperation between regulatory agencies, clinicians, and the pharmaceutical industry. Despite underreporting of adverse effects, public mistrust, and the difficulty of performing long-term safety assessments, the pandemic has strengthened the pillars for future pharmacovigilance activities. In the future, future-proofing drug safety surveillance through innovation in the acquisition of real-world evidence, standardization of global reporting protocols, and the application of AI-driven predictive analytics is likely to enhance the monitoring of drug safety. Moreover, policy responses, including adaptive regulatory mechanisms and risk communication approaches, will be critical to ensure preparedness for future public health crises. Building on these gains, global health systems can enable a stronger and forward-looking approach to drug safety monitoring, ultimately safeguarding public health in future pandemics.

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