Regulatory and Global Challenges in the Approval, Accessibility, and Monitoring of mRNA Vaccines Post COVID-19: A Review

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ABSTRACT

An important advancement in vaccine technology was made possible by the COVID-19 pandemic, which sped up the creation and regulatory licensing of mRNA vaccines. The regulatory obstacles faced in the post-pandemic era during the approval, monitoring, and post-market surveillance of mRNA vaccines are examined in this paper. Emergency usage permits allowed for quick implementation, but long-term safety, public confidence, and worldwide accessibility are still major issues. To strike a balance between quick approvals and thorough safety evaluations, regulatory bodies including the FDA, EMA, and WHO have modified their frameworks. Despite persistent underreporting and inconsistent data, post- market surveillance systems such as VAERS and EudraVigilance have been crucial in detecting adverse occurrences. In order to guarantee fair vaccine access, expedite approval procedures, and fortify pharmacovigilance infrastructure, the assessment also examines the necessity of international regulatory harmonization. Emergency usage permits allowed for rapid implementation. However, concerns remain regarding long term safety, public trust and global accessibility.

Keywords: COVID-19, Regulatory Bodies, mRNA Vaccines

1. INTRODUCTION

The COVID-19 pandemic has indeed posed an unprecedented challenge to global health systems, economies, and societies. First identified in December 2019 in Wuhan, China (Zhu etal. 2020) COVID-19 is caused by the SARS-CoV-2 virus, which, like its predecessors SARS-CoV and MERS-CoV, is believed to have crossed over from animals to humans. The virus quickly spread globally at rapid state, affecting 144 countries by mid-March 2020 (Giwa & Desai, 2020. Although COVID-19 Case fatality rate was much lower than that of MERS and SARS, its impact has been far greater due to its high transmission rate and widespread global spread. The rapid worldwide transmission and the resulting strain on healthcare systems have highlighted the importance of public health measures, vaccination efforts, and international cooperation in managing pandemics (Wells et al. 2020). The ongoing response involves not only medical interventions but also social and economic strategies to mitigate the effects on individuals and communities.

During the pandemic, mRNA vaccines were among the first to embark on clinical testing, and it is expected that they will also be

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among the first to receive complete licensing. National regulatory bodies in a number of nations have authorized the emergency use of two mRNA vaccines, which showed almost 95% efficacy in Phase 3 clinical studies (Baden et al. 2021; Polack et al. 2020) On December 31, 2020, the WHO granted emergency use listing to a COVID-19 mRNA vaccine, with the Pfizer/BioNTech vaccine being the first to obtain this validation mRNA vaccines are expected to become a foundational technology, enabling rapid development of vaccines against priority pathogens in future public health emergencies.

2. OVERVIEW OF MRNA VACCINE APPROVAL PROCESS

2.1 Historical Development

During the COVID-19 pandemic, mRNA vaccine technology, delivering mRNA encoding the SARS-CoV-2 spike protein via lipid nanoparticles- underwent rapid advancement (Khurana eta al. 2021) A key weapon in the fight against COVID-19, mRNA technology was first investigated for its potential in vaccine creation because of its speedy vaccine production after a virus's genetic sequence is determined. Using such technology, these two Pfizer-BioNTech and Moderna vaccines has shown almost 95% effectivity in phase 3 studies (Lamb 2021). In response to the public health emergency, the U.S. Food and Drug Administration (FDA) approved Emergency Use Authorizations (EUAs) for both vaccinations in December 2020 in. These authorizations permitted use of these vaccine's according to its proven safety and effectiveness in clinical trials in the United States for people 16 years and older, accordingly (Gargano 2021; Oliver 2021). Data from at least 3,000 participants was needed for a pre-licensure safety database as part of the FDA's accelerated regulatory review procedure (WHO 2020). Furthermore, the effectiveness of the studies of COVID-19 vaccines were large enough to provide safety profile for variety of age groups, including younger adults and the elderly. The EUAs were extended to include new doses and younger age groups when more data became available (Mbaeyi 2021) The purpose of this regulatory strategy was to address the urgent need for vaccines while maintaining safety and efficacy standards.

2.2 Regulatory Agencies and Global Health Agencies

The COVID-19 pandemic highlighted the approval process for mRNA vaccines, which involves various regulatory agencies and is characterized by special adaptations and challenges. These several key regulatory agencies, each contributing to ensuring the vaccines' safety, efficacy, and global accessibility. They worked together under unique challenges to facilitate the rapid development and deployment of vaccines. The following regulatory bodies & health agency are involved:

World Health Organization (WHO): Although WHO is not a regulatory body it plays a vital role in establishing international norms and standards to ensure safety, efficacy and quality of vaccines, including mRNA vaccines. In order to assist national regulatory bodies in member states, WHO initiatives seek to develop international guidelines (Knezevic et al. 2021)

European Medicines Agency (EMA): mRNA vaccines must typically receive central approval in the EU. Particularly for vaccines intended to prevent infectious diseases that are not categorized as gene therapy products, the EMA is involved in the regulatory process (Hinz et al. 2016).

U.S.FDA: The FDA has played a key role in approving mRNA vaccines, especially those created by Moderna and Pfizer-BioNTech. These vaccines' safety and efficacy were

ensured in large part by the FDA's regulatory oversight played a significant role in ensuring safety and effectiveness of vaccine, leading to the issuance of EUA during the pandemic and subsequent full approvals as additional information became available (Cao & Gao 2020).

Medicines and Healthcare Products Regulatory Agency (MHRA): One of the first regulatory bodies to grant emergency approval for the Pfizer-BioNTech COVID-19 vaccine was UK's MHRA. The distribution of vaccines in the UK and abroad was made possible by the MHRA's quick approval process, which served as a crucial illustration of how regulatory bodies responded to the pressing public health need during the pandemic (Mahase 2020) and Saudi Arabia, authorized the emergency use of mRNA vaccines. These approvals were part of a global effort to expedite vaccine distribution and administration (WHO 2020).

2.2.1 Approval Pathway

The path to final approvals after the initial EUAs necessitated additional reviews and suggestions from regulatory bodies. In the European Union, the Pfizer–BioNTech COVID-19 mRNA vaccine (BNT162b2-marketed as Comirnaty) acquired a conditional marketing authorization in December 2020, shortly following its EUA. The ongoing adaptation of vaccines to new viral types was demonstrated when the European Medicines Agency (EMA) later recommended full approval for Omicron-adapted mRNA vaccines, such as BNT162b2 and Moderna's mRNA-1273 (Spikevax) (Ellis & Weiss 2022). Different regions have different mRNA vaccine regulatory regimes. Although precise regulatory guidelines are still being developed, mRNA vaccines are centrally approved in the EU and are not categorized as gene therapies when they are intended to treat infectious diseases. As knowledge of the safety and effectiveness of vaccines grew, the FDA amended the EUA to permit additional primary and booster doses in the United States.

To further expedite access to COVID-19 vaccines and treatments globally, the WHO created two critical pathways: the WHO Emergency Use Listing (EUL) and the WHO Prequalification Program (Bolislis et al. 2021). By giving member state authorities and procurement agencies advice on vaccination performance and quality, these programs made distribution easier worldwide. The development and fair distribution of vaccines were also greatly aided by a number of international partnerships, including as the International Coalition of Medicines Regulatory Authorities (ICMRA) and the COVID-19 Tools Access Initiative (Bingwaho, Mathewos & Davis, 2021. While the COVID-19 Treatments Accelerator concentrated on guaranteeing cheap access to treatments and vaccines, particularly in low-resource areas, the ICMRA, for instance, coordinated efforts among various stakeholders to expedite vaccine development. A faster timeline for mRNA vaccines to reach the public while maintaining strict safety standards was made possible by the unprecedented speed at which vaccines were developed during the pandemic, with clinical trials being conducted at a faster pace without sacrificing quality. Normally, the regulatory process takes a sequential approach, but phases of testing were frequently conducted simultaneously to expedite vaccine availability. Following table illustrates the difference between normal approval procedure vs COVID-19 Accelerated Approval Timelines.

TABLE 1- Difference between Normal approval procedure vs COVID-19 Accelerated Approval Timelines (Burgos et al.2021)

Stage	Normal Timeline (Pre - COVID)	COVID-19 Accelerated Timeline	EU (EMA)	USA (FDA)	WHO (EUL)
Preclinical Studies	2–4 years	< 6 months	Conducted in parallel with early human trials	Conducted in parallel with early human trials	Used existing SARS-CoV-2 & mRNA platform data
Phase I – Safety	1–2 years	1–2 months	Combined with Phase II	Combined with Phase II	Relied on existing Phase I data from other agencies
Phase II – Immunogen -icity	2 years	2–3 months	Rolling review; partial data submission allowed	Rolling review; partial data submission allowed	Data sharing with EMA/FDA
Phase III – Efficacy & Safety	3–4 years	4–6 months	Conducted in parallel with manufacturing scale-up	Conducted in parallel with manufacturing scale-up	Relied on EMA/FDA Phase III data
Regulatory Review & Approval	1–2 years	2–4 weeks (EUA/CMA)	Conditional Marketing Authorization (Dec 2020)	Emergency Use Authorization (Dec 2020)	Emergency Use Listing (Dec 2020–Jan 2021)
Booster/ Variant Adaptation	1–2 years	1–3 months	Omicron-adapted CMA approved in 2022	EUA amendments for Omicron boosters in 2022	Updated EUL guidance for variant-adapted vaccines
Long-term Monitoring & PQ	Ongoing	Ongoing	Post-marketing surveillance + full approval pathways	Post-marketing surveillance + eventual Biologics License	WHO Prequalification for long-term procurement

An extremely expedited vaccine development procedure also contributed to the quick approval of COVID-19 vaccinations. Phase I (safety), Phase II (immunogenicity and additional safety), and Phase III (efficacy and safety data) are the usual steps in the vaccine development process. However, these phases were frequently conducted concurrently to speed up vaccine availability, taking use of the

enormous pool of possible subjects made available by the epidemic (CDC 2020). COVID-19 vaccine clinical trials were carried out at a never- before-seen speed without compromising the studies' quality and rigor. Furthermore, earlier studies from the creation of the SARS vaccine, along with developments in technology like reverse genetics and next-generation sequencing, enabled for quicker development times while still meeting strict safety and effectiveness requirements (Lurie et al. 2020). Notwithstanding the accelerated schedule, all conventional vaccine development stages were completed, ensuring that these vaccines met the rigorous safety and effectiveness requirements set by regulatory agencies.

3. KEY REGULATORY CHALLENGES FACED POST-COVID-19

Significant regulatory obstacles were brought about by COVID-19 pandemic, especially in the areas of vaccine safety and post-market surveillance. Although vaccines undergo extensive pre-licensure testing, the ability to detect long-term and uncommon adverse events (AEs) remains a crucial concern. After a vaccine is approved, its safety is tracked using Post-market surveillance systems, such as the Vaccine Safety Datalink (VSD) and the Vaccine Adverse Event Reporting System (VAERS), are used to monitor the safety of vaccines after approval. However, these systems rely on voluntary reporting, which can lead to underreporting of AEs and difficulties in establishing causality (Wouters et al. 2021). Effective integration of many data sources, including empirical evidence, necessitates significant financial outlay and teamwork, underscoring the need for more resilient surveillance infrastructure, especially in environments with limited resources.

Additionally, rapid vaccine development brought forth new regulatory challenges while EUAs were instrumental in accelerating vaccine safety ,they also sparked debate over how to strike a balance between safety and speed. To provide strict safety monitoring and enable quick vaccination deployment, regulatory agencies like the FDA and WHO have to modify their procedures (Thomson & Nachlis 2020). A persistent problem was the public's lack of trust in the approval process, particularly when vaccines were created and authorized faster than ever before (Rand et al. 2023). It was crucial to communicate openly the advantages and disadvantages of vaccinations in order to preserve trust in these accelerated processes.

The pandemic also underscored the need for global regulatory coordination in vaccine distribution. Differences in access and regulatory requirements impeded fair global vaccine distribution, highlighting the urgent need for coordinated international regulatory framework (Hotez et al. 2021). Regulatory agencies had to navigate these issues, balancing timely vaccine access with maintaining safety and efficacy standards. Additionally, the rapid approval of vaccines necessitated ongoing research to address uncertainties about long-term immunity and potential adverse effects, ensuring that safety monitoring remained a priority in the post- market phase (Sadeghi, Masoudi, & Khanjani 2021). Table 2 illustrates Key Regulatory Challenges Post-COVID-19.

When it comes to new vaccination and pandemic potential, it is crucial to find a compromise between maintaining stringent safety requirements and accelerating the vaccine licensing process. Rapid vaccine development can save lives, but it also raises questions about the risks of leaky vaccines and how that might affect public confidence. Important facets of this continuing discussion are examined in the sections that follow.

Table 2: Key Regulatory Challenges Post-COVID-19 (Cook et al. 2024; Savies & Rodgers 2023; Lee et al. 2024; Pepe, Novaes & Osorio-de-Castro 2021)

Area	Key challenges	Need of improvement
Clinical Research and Human Subjects Protection	Challenges with IRB reviews, informed consent, and emergency research protocols due to rapid clinical trials.	Regulatory flexibility to protect participants while enabling the rapid development of high-quality evidence.
Health and Safety Regulations	Exposed flaws in the health and safety regulatory system in the UK, especially with workforce safety.	Modernization of the regulatory regime, increased funding for enforcement, and broader recognition of health and safety as a universal workforce issue.
Radiation Safety and Inspections	Disruptions in on-site radiation safety inspections due to COVID-19, reliance on digital and remote technologies.	Adoption of digital technologies and remote systems for continued regulatory oversight.
Vaccine Regulation and Distribution	Challenges in vaccine production, affordability, allocation, and timely global distribution.	Robust global coordination to ensure timely vaccine access while maintaining safety and efficacy.
Medicines Regulation	Necessity for rapid regulatory responses in drug development, including emergency use authorizations.	Ensuring safety while accelerating drug development and monitoring adverse events.

High safety and efficacy requirements are essential to preserving public confidence in vaccines. The RTS,S malaria vaccine approved despite offering partial protection (30-40% efficacy) and requiring multiple doses, illustrates how “leaky” vaccines, if not transparently communicated about , can erode public trust (Graham & Grietens 2024). Similar dynamics arose during the COVID-19 pandemic, where early vaccine approvals under emergency pathways prioritized urgent protection over sterilizing immunity, making clear communication critical to maintain confidence. Within a year, mRNA and adenovirus vector vaccines were approved due to changes in regulatory procedures brought about by the COVID-19 pandemic (Wagner et al. 2022); nevertheless, thorough safety assessments must not be sacrificed for these modifications. Accelerated approval pathways also present challenges such as, **Infrastructure limitations in low- and middle-income nations** -Many such countries lack adequate cold-chain capacity, trained personnel, and reliable distribution

networks. These gaps can delay deployment and result in unequal vaccine access compared with high-income nations (Farlow et al. 2023. **Need for post-marketing surveillance** -Following licensure, continuous safety monitoring is essential to identify rare, long-term, or population-specific adverse events that may not have emerged during clinical trials. **Public confidence and adverse event management**- When adverse events occur, rapid investigation and transparent communication are critical to counter misinformation, address safety concerns, and sustain trust in immunization programmes. (Abdulrhaman & Abdulrahman 2024)

4. POST-APPROVAL MONITORING AND SAFETY

4.1 Adverse event reporting systems in different countries and their role in ensuring safety post-approval.

The role of adverse event reporting systems (AERS) in various countries is crucial for monitoring the safety of COVID-19 vaccines post-approval. These systems facilitate the collection and analysis of adverse events, enabling health authorities to identify potential safety signals and ensure public health safety. The following sections outline the key aspects of AERS in this context.

Many nations have established Adverse Event Reporting System (AERS) to enable healthcare professionals and the public to report adverse events following vaccination and adverse drug reactions (Imbrici et al. 2024). **VigiBase**, managed by the Uppsala Monitoring Centre in Sweden on behalf of the World Health Organization (WHO), serves as the global pharmacovigilance database, compiling reports from more than 170 member countries. Its publicly accessible interface, **VigiAccess,** has recorded approximately 24 million adverse events worldwide, with around 8 million classifies as serious (Bryant & Awrie 2024). In contrast, the Vaccine Adverse Event Reporting System **(VAERS)** is a *United States–specific* passive surveillance program jointly operated by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA). Research using VAERS has identified correlations between demographic factors and adverse events, indicating that certain reactions are more common among older individuals and specific gender groups (Choi et al.) Temporal and regional analyses of VAERS data have highlighted trends in reported symptoms, with fever, fatigue, and headache being the most prevalent adverse events (Li et al. 2022). The insights from AERS play a crucial role in shaping vaccination strategies and policy decisions, underscoring the need for continuous monitoring and potential program adjustments based on emerging safety data. However, underreporting remains a challenge, suggesting that the actual number of adverse events may be higher than documented. While AERS are essential for ensuring vaccine safety, some argue that the focus on reported adverse events may overshadow the broader benefits of vaccination in controlling pandemics Poland, Ovsyannikova & Kennedy 2020). Therefore, effective immunization programs must balance public health goals with rigorous safety monitoring to maintain public confidence and optimize vaccine deployment.

4.1.1 Role of Adverse Event Reporting Systems in Different Countries United States

Centres for Disease Control and Prevention (CDC) and Food and Drug Administration (FDA) jointly fund the Vaccine Adverse Event Reporting System (VAERS), one of the cornerstones of post-marketing safety monitoring for COVID-19 vaccines in the United States. Finding uncommon side

effects has been made possible by VAERS, which gathers and examines data on adverse events linked to vaccines (Parums 2021). The general safety of vaccines has been backed by the system's low incidence of serious side effects (Moro & McNeil 2022). The vaccination Safety Datalink, which gives active surveillance data and improves vaccination safety monitoring countrywide, and v-safe, a smartphone-based health checker, are other technologies that the CDC has put in place.

Taiwan

Taiwan emphasizes open and honest risk communication, which is crucial to maintaining public trust in vaccine safety. Taiwan's approach to vaccine safety monitoring is supported by its own Vaccine Adverse Event Reporting System, which ensures that safety information is communicated to the public in a timely and understandable manner, supporting well-informed decision-making at the individual and public health policy levels. Taiwan has achieved high immunization rates and has been successful in controlling and assessing adverse events related to COVID-19 vaccinations (Hu eta al. 2024).

Canada

In Canada, there is increased interest in using digital methods to monitor adverse events following immunization. The Canadian Adverse Event Following Immunization Surveillance System (CAEFISS) and Canada's Immunization Monitoring Program Active (IMPACT) both employ active surveillance approaches to collect data on immunization safety. By allowing citizens to actively report negative situations through internet channels, participant-centered surveillance enhances existing systems. This approach not only improves adverse event detection but also expands the local context of vaccine monitoring. Furthermore, To increase the precision and speed of reporting systems, technologically sophisticated options including mobile apps and online reporting tools are being researched (Psihogios et al. 2022).

European Union (EU)

Within the European Union, the European Medicines Agency (EMA) monitors vaccine safety using the EudraVigilance system. This unified database compiles reported adverse events following immunization from EU member states, allowing for a comprehensive view of vaccine safety across the area. The EU also places a high priority on member state cooperation to guarantee that data from each country contributes to an integrated analysis of vaccine safety. The use of data mining technologies has proven effective in identifying potential risks and trends early on, in contrast to traditional reporting techniques (Hoeve et al. 2018)

Global Perspective

The safety of COVID-19 vaccines in the post-marketing phase has been reinforced by the extremely low rates of major adverse events linked to these vaccinations reported by adverse event reporting systems worldwide. Since sharing data between nations enables a more thorough and expansive understanding of potential dangers, international collaboration on vaccination safety has proven crucial. Additionally, the use of data mining techniques by systems like the FDA's Adverse Event Reporting System is a promising strategy for efficiently identifying potential adverse drug occurrences. Both the COVID-19 vaccine and future pandemic responses will benefit from these reporting system enhancements, particularly when it comes to monitoring vaccinations during the initial stages of global rollouts for emerging illnesses (Guo et al. 2022).

4.2 Ongoing risk-benefit analysis used by regulatory bodies

As new information becomes available, regulatory agencies continuous risk-benefit analysis is essential to guaranteeing the effectiveness and safety of vaccinations. This procedure entails ongoing evaluation and monitoring of the advantages and disadvantages of vaccinations, especially in light of the COVID-19 pandemic. Because vaccination safety data is dynamic, regulatory bodies like the European Medicines Agency (EMA) have put in place strong frameworks to make this analysis easier. For instance, In April 2021, the EMA's risk-benefit assessment of the AstraZeneca COVID-19 vaccine (Vaxzervria) concluded that very rare cases of thrombosis with thrombocytopenia syndrome were linked to the vaccine Greinacher et al. 2021. For this EMA updated product information, restricted use in certain age groups in some countries, but maintained that benefits outweighed risks for most adults during high transmission period.

The balance between risks and benefits must be continuously assessed in order to make well- informed decisions on vaccinations and public health initiatives. This strategy makes sure that any possible negative effects of the interventions - such as adverse effects, logistical difficulties, or social repercussions are outweighed by the positive public health outcomes, such as the avoidance of serious disease or death.

Risk-Benefit Analysis of Vaccines:

The COVID-19 vaccine is one of the most crucial tools for stopping the virus's spread and reducing the severity of illness. Regulatory agencies have carried out extensive risk-benefit analyses to evaluate the efficacy and safety profiles of various immunizations (Son et al. 2022). A key example of this kind of research is multi-criteria decision analysis (MCDA), a quantitative method that evaluates several elements simultaneously. The prevention of COVID-19 infection, the avoidance of severe cases, and the incidence of adverse effects were all taken into account in the case of COVID-19 vaccines. For example, in April 2021, the U.S.FDA temporarily paused the use of the Johnson & Johnson COVID-19 vaccine after rare cases of thrombosis with thrombocytopenia syndrome were detected. Following a rapid review of available data, the agency determined that the benefits outweighed the risks for most adults and resumed use with updated warnings in the EUA fact sheet.

The analysis repeatedly shown a positive balance between the risks (such as mild to moderate symptoms or extremely rare severe events) and the benefits (such as protection against infection and severe disease) for vaccines like mRNA-1273 (Moderna) and BNT162b2 (Pfizer-BioNTech) (Thompson 2021). These results supported the decision to keep using them all over the world, assisting healthcare executives and legislators in directing immunization programs and giving priority to groups that are most at risk. This kind of study is essential for making sure that the advantages of widespread vaccination programs exceed any possible drawbacks, which is still a critical public health priority.

Regular Immunization Throughout the Epidemic:

In addition to COVID-19 vaccination campaigns, many nations have faced challenging choices regarding the continuation of regular immunization programs, especially during the pandemic. During the COVID-19 pandemic, for instance, a risk-benefit analysis was carried

out in Africa to determine whether routine childhood vaccines should continue. This study concluded that the benefits of continuing routine childhood immunizations greatly outweighed the risk if additional COVID-19 exposure, estimating that for every excess COVID-19 death caused by exposure during immunization visit (Abbas et al. 2020). This finding reinforces the principle underlying mRNA vaccine emergency and conditional approvals: in a high burden infectious disease scenario, the rapid deployment of effective vaccines is justified when the expected public health benefits vastly exceed potential risks. The same benefit-risk reasoning guided global regulatory bodies in granting accelerated authorizations for COVID-19 mRNA vaccines.

5. REGULATORY APPROACHES TO MRNA VACCINE INNOVATION

The regulatory environment surrounding mRNA vaccines is complex and dynamic, reflecting the novel nature of this technology. Since there are currently no specific guideline for mRNA vaccines in the EU or around the world, It is important to examine the existing regulatory frameworks and identify the challenges they present. Although mRNA technology is widely used, regional regulatory procedure differs and WHO has not set precise criteria for mRNA vaccines. It normally needs central approval from EU, but inconsistent practices have resulted from a lack of specific rules (Ellis & Weiss 2022). The rapid development and certification of mRNA vaccines during COVID-19 pandemic raised significant regulatory concerns, especially when conventional frameworks were circumvented to address pressing public health demands (Banoun 2023). Consequently, calls were made for longer-term research, more thorough safety assessments, and a more precise definition of mRNA vaccines, which are regulated as vaccinations but are sometimes viewed as gene treatments, raising concerns about safety and compliance.

In accordance with current human medicine regulations, the UK has taken a flexible stance and granted a temporary regulatory license (Bouderhem 2023). These regulatory flaws have raised concerned about safety, efficacy and quality control of mRNA vaccines, particularly in low and middle-income countries with weak infrastructure (de Andrade et al. 2015). However, using mRNA as a platform technology makes it easier to design treatments for various illnesses, which supports changing current laws to take into account the special characteristics of mRNA products (Naik & Peden 2020). In order to promote predictable development routes that could lower costs and speed up access to vaccines, particularly for pandemics and rare diseases, international efforts including WHO initiatives are working to establish global norms and standards (Liu et al. 2021). International convergence and cooperation between governments, business, and academia are essential for the future of mRNA vaccine regulation in order to address issues like stability, storage as well as security. This continuous discussion will be crucial to creating strong regulatory frameworks that strike a balance between public safety and innovation, guaranteeing that mRNA technology keeps improving while upholding strict quality and efficacy standards.

6. GLOBAL REGULATORY HARMONIZATION

Standardized regulatory standards are urgently needed to speed up international vaccination clearance processes, as the COVID-19 pandemic has shown. The pandemic highlighted the delays and inefficiencies caused by different countries regulatory policies, which could obstruct the

rapid development and distribution of vaccines. The time and complexity required to cross several regulatory environments can be decreased with the use of standards, potentially resulting in quicker clinical development and early access to life saving vaccination (Lacey & Mitchell 2023). The lessons learned emphasize how important it is for regulatory agencies to collaborate in order to provide timely vaccine access, particularly for LMICs. Many countries used accelerated approval processes, including conditional marketing licenses and EUA, to expedite vaccine supply during the epidemic. By facilitating the faster distribution of vaccines than would be feasible through conventional methods, these approaches illustrated the potential benefits of shortened regulatory techniques during international health emergencies (Mahoney, Hotez, & Bottazzi 2023). LMICs can improve their regulatory capacities and provide equitable access to vaccine in times of medical emergency by developing similar regulatory frameworks. Standardization standards can also reduce effort duplication, allowing for faster approvals in different areas. The pandemic has also highlighted the significance of regulatory convergence and co-operation, particularly in Asia-Pacific region, where increased collaboration among national regulatory bodies has facilitated the sharing of resources and expertise., which has somewhat aided in harmonizing policies and practices[60]. This partnership could lead to more efficient vaccination approval processes and better preparation for further emergencies. This epidemic has also sparked initiative to grant LMIC regulatory authorities' stricter regulatory status in order to increase their ability to manage future crises. Future pandemic will require ongoing collaboration between international regulatory bodies to ensure preparedness and timely access to drug and vaccines (Soumyanarayanan 2021).

6.1 Regional Variations

The regulatory environment around mRNAvaccines is complex, influenced by several regional frameworks and obstacles. Even though the US and EU have made great progress in vaccine regulation, emerging nations still confront particular difficulties, particularly with regards to approval processes and distribution infrastructure.

United States: The FDA has implemented a simplified procedure for certifying mRNA vaccines in the US under the EUA. This strategy, which is based on established clinical trial data, makes it possible to quickly distribute vaccines in times of medical emergencies such as the COVID-19 pandemic. However, there has been lot of debate regarding how to balance speed and thoroughness of safety review, especially in early phases of vaccine rollouts (Saeed et al. 2024). Although the EUA procedure is intended to allow for quick response in emergency situations, it also entails review of long-term safety data.

European Union: Once approved, mRNA vaccines are made available in all EU member states thanks to the EU's centralized approval process run by the European Medicines Agency (EMA). This process, often regarded as more stringent than the American one, ensures that safety and efficacy are evaluated in detail. regulatory gaps are created by the EMA's framework's lack of particular standards for mRNA vaccines, which makes it challenging to quickly adopt innovative vaccination technologies. This has sparked worries about the necessity of additional specialized laws to handle the particular difficulties presented by mRNA vaccinations (Guerriaud & Kohli 2022).

Asiatic and African Emerging Markets

In emerging market the regulatory landscape pertaining to mRNA vaccines varies significantly. Many countries in Asia and Africa relied on international collaboration and WHO guidelines for the licensing and distribution of vaccines. This region usually rely on WHO emergency use lists or approvals from more respectable regulatory bodies like the FDA or EMA because they lack specialized regulatory frameworks (Patel et al. 2023). This dependence may cause delays in the distribution and availability of vaccines, underscoring the necessity of strengthening regulatory systems' competence in these areas.

6.1.1 Challenges in Emerging nations:

In developing countries, the logistical and regulatory issues of mRNA vaccine distribution pose additional difficulties.

Regulatory Gaps: Many underdeveloped countries lack established protocols for mRNA vaccine approval. Because of this legislative ambiguity, different countries have different methods, which slows down access to vaccines. In other countries with less stringent regulations, questions about the efficacy and safety of vaccines may surface (STati et al. 2023).

Cold Chain and Dissemination: It is particularly challenging to distribute mRNA vaccines, which require ultra-cold storage, in places with inadequate infrastructure, such as parts of Africa and Asia. Since many of these locations lack the cold chain logistics needed to transport and store the vaccines securely, it is difficult to ensure their efficacy once they get at their destination (Nachega et al. 2021 & Dicko et al. 2000). These practical difficulties make distribution of vaccines to vulnerable populations. This challenge includes the scarcity of ultra cold freezers (-70 degree C), unreliable electricity, limited refrigerated transport, and a shortage of trained staff. Potential remedies include deploying solar powered cold storage, developing regional hub with reliable power and promoting vaccine formulation stable at 2-8 degree C (Farlow et al. 2023).

Observation & Monitoring: In many developing countries, the absence of robust healthcare data systems further hinders post-vaccine surveillance. Without sufficient control, it is difficult to track adverse effects and assess the long-term safety of mRNA vaccines once they are introduced (Kadali et al. 2021& Nassar 2023). This infrastructure deficiency may cause delays in reacting to emerging safety concerns.

Regardless of economic standing, international health organizations might guarantee that all nations have prompt access to state-of-the-art vaccines by coordinating regulatory procedures and infrastructure assistance. The significance of worldwide regulatory harmonization is underscored by these disparities in vaccination distribution and regulation. Institutions like the World Access to vaccines in low-income nations has been made easier by the WHO and Gavi, but more has to be done to establish uniform approval procedures. Inconsistencies could be lessened via a worldwide regulatory framework, improving emerging nations' ability to handle health emergencies (Ghadanian & Schafheutle 2024).

7. FUTURE DIRECTIONS AND RECOMMENDATIONS

Maintaining public trust in immunization programme guaranteeing the long-term safety of vaccine depends heavily on post marketing surveillance. This entails keeping an eye on adverse events after vaccination and resolving any safety issues that surface post vaccine distribution and licensing. The main obstacles, solutions, and future paths for enhancing post-market surveillance of vaccine safety are shown in Table 4.

Regulatory innovation refers to the adoption of novel regulatory tools, processes, or frameworks such as adaptive approval pathway or digital submission platform- to address emerging medical technologies more effectively. Regulatory agility describes the ability of regulatory authorities to adapt and expedite procedure. For example, by implementing rolling reviews or accelerated assessment, while maintain rigorous standard for safety, efficacy and quality. is crucial to accelerating the approval process for upcoming mRNA vaccines that target newly developing infectious illnesses. Regulatory agilities, which have been shown to reduce review periods without compromising efficacy and safety, are one tactic (Geraci 2023). During the COVID-19 pandemic, reliance techniques and regulatory agility significantly reduced review durations for vaccines like Pfizer/BioNTech's BNT162b2, demonstrating their effectiveness in improving public health outcomes. Moreover, international initiatives by organizations such as the WHO aim to establish global guidelines for the manufacturing and quality control of mRNA vaccines, encouraging the convergence of regulatory practices and supporting national regulatory organizations (Gouglas, Christodoulou & Hatcherr 2023).

In order to speed up the licensing of future mRNA vaccines for newly emerging infectious diseases without compromising safety, regulators could implement a number of important developments. One such strategy is the use of "rolling reviews," which allow authorities to evaluate clinical trial data as it becomes available instead of waiting for all data to be submitted at once (Hofner et al. 2024). This can significantly shorten the clearance time while ensuring that data integrity and safety criteria are met. (Ranga, Naved, & Thakker 2024)

Table 4: Key Challenges, Strategies, and Future Directions for Strengthening Post-Market Surveillance of Vaccine Safety (Ghadanian & Schafheutle 2024; Lao et al. 2022; Hodel et al. 2024; Standaert et al. 1995; Shen et al. 2023; Torcel-Pagnon et al. 2019; Kim, Marks & Clemens 2021)

Area	Challenges	Strategies for improvement	Future direction
Data Quality and Coverage	- High quality data from large populations required. - Inconsistent data standards and privacy concerns.	-Develop large, linked databases across countries. - Harmonize data collection and analysis methods.	- Strengthen global collaboration for better data exchange.
Study Design and Bias	- Traditional study designs (cohort, case-control) may have selection and confounding biases.	- Explore newer designs like self-controlled case series. - Validate and compare new designs for real- world use.	- Continuously improve study designs through validation and real-world application.

Area	Challenges	Strategies for improvement	Future direction
Underreporting and Public Engagement	- Significant underreporting of adverse events. - Lack of robust reporting mechanisms.	- Improve public engagement and encourage contributions from healthcare workers and the public.	- Develop better reporting systems (e.g., QR codes) to boost participation.
Surveillance Systems	- Passive surveillance systems lack timeliness. - Difficult to detect safety signals in real-time.	- Develop active surveillance systems using electronic health records and claims data. - Utilize near real-time surveillance for faster detection.	- Implement technological innovations to improve surveillance and reporting efficiency.
Advanced Analytical Methods	- Difficulty in accounting for seasonal variations and reference risks.	- Implement advanced statistical methods (e.g., seasonality- adjusted sequential tests).	- Continuously refine analytical methods to ensure reliable safety assessments.
Public-Private Collaborations	- Limited coordination between public and private sectors in surveillance efforts.	- Strengthen public-private partnerships to improve governance and data analysis.	- Enhance transparency in governance frameworks for better collaboration.
Global Coordination	- Global vaccine monitoring systems may lack equity and coordination.	- Enhance global coordination to ensure equitable vaccine distribution and monitoring.	- Ensure global efforts are aligned to strengthen surveillance and

Establishing adaptable regulatory pathways would also be beneficial, enabling regulators to approve vaccinations for use in emergency scenarios while further data is obtained. These strategies would enable quick deployment in emergency situations

while monitoring ongoing trials to ensure ongoing monitoring of vaccine safety and effectiveness.

Enhancing international collaboration and standardizing regulatory processes across countries will also unable faster international approvals and more efficient data exchange. While safety remain the first priority , using digital technologies for pharmacovigilance and real time data monitoring may potentially speed up regulatory decision making (Eghaghe etal. 2024). Additionally, encouraging the creation of platform technologies which can be swiftly modified to target various pathogens will improve the speed at which vaccines for a range of infectious diseases may be developed and approved.

7.1. Standardization of Global Approaches

The standardization of global approaches is crucial for facilitating international trade, enhancing economic development, and expediting the approval and distribution of products and services worldwide. Harmonized international standards can reduce trade barriers, improve data sharing, and support the development of global supply chains.

The Value of International Standardization

Economic Impact: Trade volumes and economic growth are greatly enhanced by standardization. Harmonized standards promote the development of global supply chains and lower trade barriers between countries, both of which are critical for economic expansion.

Trade and Market Access: One of the biggest barriers to global trade is the existence of disparate product standards. The cost and demand structure of exporting can be drastically changed by standardization, which promotes more seamless trade flow (Schmidt & Steingress 2022).

Drivers and Challenges in Standardization

Participation in Standardization: Nations such as the US and China have demonstrated a calculated approach to joining international standardization organizations such as ISO, which aids in determining technical trends and bolstering global influence (Blind & Von Laer 2022).

Technical and Regulatory Difficulties: Digitalization has caused several sectors to converge, necessitating a multidisciplinary understanding of standardization to address technical and regulatory challenges effectively (Kanevskaia 2019).

The creation of harmonized international standards is vital for reducing trade barriers, enhancing economic development, and facilitating the global distribution of products and services. Strategic participation in standardization processes and a multidisciplinary approach are essential for addressing the challenges and leveraging the benefits of global standardization.

8. CONCLUSION

During COVID-19, the quick development and approval of mRNA vaccines brought to light the advantages and disadvantages of the current regulatory systems. Rapid deployment was made possible by EUAs, but issues with public confidence, long-term safety, and access inequities around the world still exist. Although post-market surveillance systems encountered challenges like underreporting of adverse events, regulatory bodies such as the FDA, EMA, and WHO were crucial in guaranteeing the safety and effectiveness of vaccines. Harmonizing regulatory standards globally to expedite approvals and guarantee fair vaccination distribution is a significant post-pandemic problem. The safety and effectiveness of mRNA vaccines are maintained by continuous risk-benefit studies, even in the face of rare side effects. Examples of creative regulatory strategies

that have been effective in accelerating vaccine approvals without compromising safety include rolling reviews and real-time data monitoring.

It will be crucial to strengthen post-market surveillance, improve international regulatory cooperation, and use digital technologies for immunization monitoring. The pandemic has brought attention to the need for strong, adaptable regulatory frameworks that balance rapid vaccine deployment with public safety and trust. A global coordinated approach will be required to fully realize the potential of mRNA vaccine technology and prepare for impending health crises.

9. Conflict of Interest

None.

10. Financial Support

None.

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