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Challenges Faced by States and the WHO in Efficiently Regulating the Use of mRNA Vaccines †

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Abstract: According to the World Health Organization (WHO), there is no formal regulatory guidance specifically for mRNA-based vaccines. However, the WHO provides information and regulatory considerations regarding key aspects of the manufacture and quality control, and nonclinical and clinical evaluation, of preventive mRNA vaccines against infectious disease for human use. The global research and development of mRNA vaccines have been prodigious over the past decade, and the work in this field has been stimulated by the urgent need for rapid development of vaccines in response to an emergent disease such as the current COVID-19 pandemic. In the European Union (EU), no regulatory guidelines presently exist that specifically address mRNA-based vaccines. The existing regulatory framework, however, clearly defines that mRNA-based vaccines in most cases have to be centrally approved. In the UK, both mRNA vaccines were granted temporary regulatory authorization under Regulation 174 of the Human Medicine Regulations 2012. The potential of mRNA vaccine as a technology to rapidly respond to public health emergencies of infectious diseases, in addition to application for prophylactic vaccines for additional infectious diseases, have underscored the need for international regulatory convergence for mRNA vaccines. The challenges faced by states in the use of mRNA vaccines include not only regulatory gaps but also technical issues such as the need for cold storage and transportation.

Keywords: WHO; mRNA vaccines; COVID-19; infectious diseases; regulations

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1. Introduction

The mRNA vaccines played a crucial role in tackling the COVID-19 pandemic [1]. The Pfizer/BioNTech and Moderna mRNA vaccines were generally authorized for emergency [2] use less than one year after the emergence of COVID-19 [3], which demonstrated an incredible speed in COVID-19 understanding. Emerging mRNA technologies have been studied for their potential qualitative impact against diseases such as rabies, influenza, Zika, HIV and cancer, as well as for veterinary purposes [4]. According to research, mRNA vaccines do not represent a threat to global health: they are an effective and safe technique to combat COVID-19 [5]. There is no scientific evidence that mRNA vaccines are a potential threat to human health [6] or the environment. Indeed, '[R]andomised trials have shown high efficacy of mRNA vaccines against symptomatic COVID-19' [7]. However, the precautionary principle should apply here in order to determine potential harm to humans as a global health standard [8]. Moreover, mRNA vaccines do not alter DNA [9]; they do not enter the nucleus of the cells. The mRNA technology only instructs the cells to make a harmless protein from the COVID-19 virus, which will trigger an immune response. The mRNA vaccines degrade quickly and only stay in the body for a couple of days. The mRNA technology is also characterized by its specificity [10]; mRNA vaccines only target the spike protein of the COVID-19 virus [11], which is essential for the virus to enter human cells.

The spike protein is not found in any other organism, so the vaccine does not affect any other part of the body or the environment. Another misconception about mRNA vaccines is related to an alleged novelty [12]. They have been studied for decades [13] and have been used in human trials for cancer vaccines since 2011 [14]. According to Rosa et al., 'unlike attenuated or inactivated vaccines, mRNA is precise as it will only express a specific antigen and induce a directed immune response' [15]. The mRNA platform technology demonstrated its safety and effectiveness [16]. The two mRNA vaccines authorized by regulatory agencies such as the Food and Drug Administration (FDA) in the US and the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK [17], Pfizer/BioNTech and Moderna, have been tested in large-scale clinical trials involving tens of thousands of volunteers [18]. They have shown to be at least 90% effective [19] at preventing people from falling ill with COVID-19, and very good at preventing serious or fatal cases.

Regulatory challenges need also to be tackled at both national and international levels. There are today no specific EU regulations nor guidelines relating to the challenges posed by mRNA-based vaccines. However, EU law explicitly requires that mRNA-based vaccines have to be approved by a central regulatory authority [20]. Moreover, the WHO did not release specific guidelines or any legally binding rules dealing with mRNA-based vaccines [21]. The WHO only provides information and regulatory considerations regarding key aspects of the manufacture and quality control, and nonclinical and clinical evaluation, of preventive mRNA vaccines against infectious disease for human use [22]. The need for international regulatory convergence for mRNA vaccines is an absolute necessity and could be achieved by the WHO in accordance with its constitutional mandate to tackle pandemics and global health crises [23].

2. Challenges and Ethical Concerns Faced by States and the WHO in Efficiently Regulating the Use of mRNA Vaccines

States are facing numerous challenges regarding the development and use of mRNA vaccines including not only technical issues but also ethical and regulatory challenges (see Table 1 below).

Table 1. Challenges and ethical concerns posed by the use of mRNA vaccines.

Main Challenges Posed by the Use of mRNA Vaccines
1. Cold-chain storage
2. Scalability and manufacturing
3. Public acceptance and trust
4. International coordination and cooperation
5. Legal and ethical issues (conflicts of interest)
6. Technology transfer to low- and middle-income countries (LMICs) [24]
7. Capacity building
8. Stringent IP rules and absence of real IP waivers for LMICs [25]
9. The use of fetal cell lines in the development and testing of some mRNA vaccines
10. Consent and privacy issues related to the origin of some cell lines
11. Equity and justice issues related to the access and distribution of mRNA vaccines

The Pfizer-BioNTech vaccine needs to be stored at −90 °C to −60 °C [26]. The Moderna vaccine can be stored at −20 °C [27]. The need for cold storage and transportation can make it difficult to distribute the vaccine to remote areas or areas with limited infrastructure, especially in low- and middle-income countries (LMICs). The mRNA technology platform comes with new technical issues; these new vaccines require an extreme cold-chain storage, which affects the distribution of the vaccines worldwide, particularly in warm countries or

those without reliable cold-chain storage. This also impacts the stability and degradation of the mRNA vaccine [28].

Scalability and manufacturing are also technical challenges, which require high-quality and consistent production of large quantities of mRNA vaccines in a short time. According to Whitley et al. [29], there is a 'need for a scalable clinical-enabling manufacturing process to produce such products, and robust analytical methods to demonstrate safety, potency, and purity. To date, production processes have either not been disclosed or are bench-scale in nature and cannot be readily adapted to clinical and commercial scale production.' As noted by Rosa et al., 'SARS and Ebola epidemic outbreaks and, more recently, the CODVID-19 pandemic, show that many of the current platforms are not well suited for a very fast, efficient, and cost-effective response.'

When developing new medicines and vaccines especially in times of pandemics, public acceptance and trust is a fundamental factor in the success of large-scale vaccination programs. Public acceptance also depends on the availability, accessibility and affordability of the vaccines, as well as the communication and education efforts to inform the public about the safety, efficacy and benefits of the mRNA vaccines [30]. There is also a need to address vaccine hesitancy, misinformation and anti-vaccine sentiments [31].

The legal [32] and ethical issues following the use of mRNA vaccines include concerns about safety, efficacy and long-term effects. There are also concerns about access to the vaccine and distribution. On 18 August 2023, the WHO Strategic Advisory Group of Experts on Immunization (SAGE) released amended and updated interim recommendations for the use of the Moderna COVID-19 (mRNA-1273) vaccine against COVID-19; also, SAGE recommended that both Pfizer-BioNTech and Moderna vaccines could be used in children aged 6 months and older [33]. States and key international organizations such as the WHO have to cooperate and coordinate their actions through harmonized guidelines and legally binding rules; international coordination and cooperation involve the harmonization of regulatory standards, the sharing of data and information, the allocation and distribution of vaccine doses and the monitoring of vaccine safety and effectiveness. The WHO plays a key role in facilitating these aspects through its various mechanisms, such as the Emergency Use Listing, the COVAX Facility, the COVID-19 Vaccine Delivery Partnership and the COVAX No-Fault Compensation Program.

There are some ethical concerns with mRNA vaccines, but they are not related to the safety or efficacy of the vaccines themselves:

- The use of fetal cell lines in the development and testing of some mRNA vaccines [34]. Some religious groups, such as some Catholics, have objected to the use of cell lines derived from human fetuses aborted electively in the 1970s and 1980s but also during the COVID-19 pandemic [35].
- The consent [36] and privacy [37] issues related to the origin of some cell lines. Some cell lines, such as HeLa cells, were obtained from human tissues without the knowledge or consent of the donors or their families.
- The equity and justice [38] issues related to the access and distribution of mRNA vaccines. There is a global imbalance in the availability and affordability of mRNA vaccines, which are mostly produced and purchased by high-income countries [39].
- Technology and research challenges require adequate international cooperation, especially for developing countries which cannot necessarily afford to develop mRNA vaccines. Mechanisms should be implemented by the WHO according to its constitutional mandate to regulate global public health and threats such as the COVID-19 pandemic. Examples of cooperation mechanisms could be COVAX for instance.
- Risk assessment and mitigation. The mRNA technology is relatively new which requires appropriate risk assessment strategies at national, regional and international levels. Researchers have to conduct studies to determine if the newly developed mRNA vaccines do not represent a greater risk for the population or a given group. The Sudden Adult Death Syndrome related to the mass vaccinations using mRNA

during the COVID-19 pandemic is an illustration of interrogations and concerns raised by the scientific community [40].

- Political concerns and potential risks of conflicts of interest. Key players such as the European Union, the WHO, the United Nations should address issues related to conflicts of interest and ensure that regulatory authorities and international organizations do have explicit guidelines and regulations to prevent situations of conflicts of interest. Appointing individuals from the private sector to leading positions in international organizations or in regulatory authorities such as the WHO or the EU should reasonably raise a red flag as the principles of independence and impartiality could be undermined.

3. The WHO's Constitutional Mandate to Regulate the Use of mRNA Vaccines

The WHO is the leading global health authority that provides guidance and coordination for health matters within the United Nations system [41]. The WHO has the mandate to regulate the use of mRNA vaccines for COVID-19 through its various mechanisms, such as:

- The Emergency Use Listing (EUL) procedure, which is 'a risk-based procedure for assessing and listing unlicensed vaccines, therapeutics and in vitro diagnostics with the ultimate aim of expediting the availability of these products to people affected by a public health emergency' [42]. The WHO has issued EULs for several mRNA vaccines, such as Pfizer/BioNTech, Moderna and CureVac, based on rigorous evaluation of their quality, safety and efficacy data [43].
- The Strategic Advisory Group of Experts (SAGE) on Immunization, which is the principal advisory group to WHO for vaccines and immunization. SAGE issues recommendations and guidance on the use of vaccines in populations, such as priority groups, dosing intervals, contraindications and precautions [44].
- The COVAX Facility, which is a global initiative co-led by WHO, Gavi and CEPI to ensure fair and equitable access to COVID-19 vaccines for all countries. COVAX aims to accelerate the development and manufacturing of COVID-19 vaccines and distribute them to participating countries according to a transparent allocation framework. COVAX has secured agreements with several mRNA vaccine manufacturers to supply doses to low- and middle-income countries (LMICs). However, the launch of COVAX did not meet all its expectations and failed to provide COVID-19 vaccine doses to LMICs [45]. Some researchers also considered the COVAX mechanism as a failure of the international community to help LMICs access vaccines and other essential medicines [46] and a 'vaccines apartheid'.
- The COVID-19 Vaccine Delivery Partnership (CoVDP), which is a collaboration between WHO, UNICEF and Gavi to support countries in accelerating vaccine delivery, to save lives and prevent people from becoming seriously ill. CoVDP provides technical assistance, guidance and tools to help countries plan, prepare and implement vaccination campaigns. CoVDP recently transitioned its delivery support back to the core agencies (Gavi, UNICEF and WHO) by the end of June 2023 [47].
- The COVAX No-Fault Compensation Program, which is the world's first and only international vaccine injury compensation mechanism. The purpose of this Program is to support COVAX in delivering safe and effective COVID-19 vaccines to vulnerable and/or high-risk populations in 92 LMICs. The Program covers rare but serious adverse events associated with any COVID-19 vaccine distributed through COVAX [48].

Several solutions are offered to states and the WHO to regulate the use of mRNA vaccines (see Table 2 below). There is an urgent need for harmonization at both regional and international levels. WHO members should adopt new legally binding rules to ensure that all stakeholders—public and private actors—are bound by the same standards and ethical principles in terms of research and development, deployment and commercialization of mRNA vaccines. International organizations such as the United Nations (UN) and

the WHO should optimize the use of their attributions under the UN Charter and the International Health Regulations (IHR) to cooperate accordingly.

Table 2. Solutions to adequately regulate the use of mRNA vaccines at both national and international level.

Potential Solutions to Adequately Regulate mRNA Vaccines
1. Establishing clear guidelines and standards under WHO
2. Strengthening regulatory oversight
3. Promoting transparency and accountability
4. Encouraging industry self-regulation
5. Fostering international cooperation
6. Ethics: necessity to adopt rules of professional conduct to prevent conflicts of interest

4. Examples of States Regulations and International Guidelines for the Use of mRNA Vaccines

In the United States, the FDA has regularly amended the emergency use authorizations (EUAs) of the Moderna and Pfizer-BioNTech COVID-19 bivalent and monovalent mRNA vaccines to simplify the vaccination schedule for most individuals. On 11 September 2023, the FDA released new guidelines and decided to update the list of approved mRNA vaccines, which 'include [now] a monovalent (single) component that corresponds to the Omicron variant XBB.1.5' [49].

In the European Union, the European Medicines Agency (EMA) has granted conditional marketing authorizations (CMAs) to four COVID-19 vaccines, including two mRNA vaccines: Comirnaty (Pfizer/BioNTech) and Spikevax (Moderna) [50]. The CMAs are valid for one year and need to be renewed annually. The EMA has also approved a booster dose of Comirnaty for people aged 12 years and older, at least six months after completing the primary vaccination course [51].

5. Conclusions

On 5 May 2023, WHO Director-General Tedros Adhanom Ghebreyesus officially decided to end the COVID-19 public health emergency of international concern (PHEIC) [52]. However, he invited states party to the International Health Regulations (IHR) to pursue their efforts in tackling the COVID-19 pandemic by keeping track of new variants and death tolls as well as reporting information surveillance to the WHO. Here, it is important to highlight international cooperation as a lever towards vaccine equity [53]. The WHO has the ability to be a catalyzer and provide the adequate legal framework in the field of mRNA vaccines and their development. Under the WHO, legal tools that may help LMICs easily access new vaccines exist but they need to be amended in order to achieve vaccine equity and tackle efficiently any future global health crisis.

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