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Review Article

A Review on Strategies for COVID-19 Vaccine Development and Regulatory Requirements

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Abstract

Scientists first identified Human Coronavirus in the year 1965. Then, a study was performed on different human and animal viruses, which were named based on their crown-like appearance. Human coronaviruses are responsible for many children's upper respiratory tract infections. At least five new human coronaviruses have been identified since 2003, including the severe acute respiratory syndrome (SARS) coronavirus, which caused significant morbidity and mortality.[1] Per NL and the New Haven, the virus associated with upper and lower respiratory tract disease and likely common human pathogens are identified as the Group-I coronaviruses (SARS- CoV-I). The novel coronavirus (SARS-CoV-II), which appeared in Wuhan, China, in December 2019, is responsible for Coronavirus disease 2019 (COVID-19) and causes respiratory symptoms that can feel like a cold, flu, or pneumonia. Geographical transmission of the virus and the sudden increase in cases are much faster than SARS and Middle East respiratory syndrome (MERS). COVID-19 is the first global pandemic caused by a coronavirus causing outbreaks in 211 countries. The vaccine against COVID-19 is an effective prophylactic strategy for controlling and preventing the virus. The vaccine is being developed in about 90 institutions worldwide. This research paper focuses on COVID-19 vaccine development strategies implemented by various institutions and pharmaceutical companies worldwide and regulatory requirements for vaccine approval.

Keywords: Human Coronavirus, Severe Acute Respiratory Syndrome (SARS), COVID-19 vaccine development strategies

1. INTRODUCTION

Novel SARS-CoV-II (COVID-19) emerged as a threat to public health; strategies for COVID -19 vaccine development and country-specific regulatory requirements played a significant role, as no treatments were available for the COVID-19 vaccine. The SARS-CoV-II caused havoc in the USA, Europe, China, and other countries, causing 1 million deaths and 50 million infections. The shortage of medicines and oxygen supply at healthcare facilities caused several hundred death per day around the world. There was a need to develop a safe vaccine that would save lives, time, and money—giving people an option to receive the vaccine when necessary was crucial. Collaboration between the government and pharmaceutical companies while adhering to regulations to create safe and effective vaccines played a crucial role in vaccine development.

2. MATERIALS & METHOD

2.1. SARS-CoV-II

SARS-CoV is a single-chain RNA corona belonging to the CoV coronavirus family of Coronaviridae and was discovered in the 1960s[31]. A novel member of human CoV that emerged in Wuhan, China, is formally named SARS-CoV-II. This is a unique strain of RNA viruses that has not been previously observed in humans. SARS-CoV-II typically causes respiratory and gastrointestinal sickness in both humans and animals. The virus can be transmitted through aerosols and direct/indirect contact, as well as during medical cases and laboratory sample handling. Specific structural proteins, which might be found on the virus's surface, play an essential role in the pathogenesis and development of the complications.

2.1.1. Structure of SARS-CoV-II

The viral genome contains Spike (S), envelop (E), Membrane (M), and nucleocapsid (N) antigenic proteins. E and M form the virus's outer membrane, while the N protein forms an RNA structure for virus replication. Protein S is shaped like a crown-like spike that binds to the viral angiotensin-converting enzyme (ACE)-2 receptor on human cell surfaces. Protein S is the major antigen for receptor recognition, adhesion, and virus entry. Vaccine development relies on the body's protein S defense response to protect against SRAS-CoV-II [21,31].

2.2. New drug development Process

There are five critical steps in the US FDA drug development process, including many phases and stages within each of them. The phases of new drug development include Discovery and Development, Preclinical Research, Clinical Development, FDA Review, and FDA Post-Market Safety Monitoring.

Other than the product development path for the seasonal influenza flu vaccine, typical vaccine development for a novel pathogen is expected to take several years of research to fully understand the viral structure-function relationship and the critical protective host immunities that can define vaccine antigen targets.[32]

2.3. Traditional Approach to Vaccine Development Process

Usually, the typical time needed to develop a vaccine using conventional methods is 15 years. Starting with exploratory work on vaccine design and evaluation in animal models, followed by a formal phase involving more extensive preclinical experiments, designing a vaccine production process, and conducting legal toxicology studies as a part of preclinical research. Clinical trials include phase I trials to generate an initial safety profile of the vaccine candidate and obtain preliminary immunogenicity data, after which an Investigational New Drug (IND) application is filed. In phase 2 clinical trials, the optimal dose is specified; in phase 3 clinical trials, the efficacy and safety of a drug are determined. Finally, a biologics license application is submitted to the appropriate regulatory agencies (such as FDA) if the results meet the predetermined endpoints. An additional year or two may be needed for licensing; significantly more information is required.

2.4. Past Vaccine Knowledge and New Technology

Since last century, remarkable scientific and technological advancements have significantly contributed to the increased efficacy of vaccines and the accelerated rate at which they can be manufactured. Industry and academic vaccine development experience have accelerated COVID-19 vaccine development. Since the 1960's coronaviruses, which cause mild to moderate upper respiratory tract illnesses like the common cold, have been studied. SARS- CoV-I and MERs CoV, both deadly coronaviruses, emerged from animal resources in the past two decades[18]. These viruses resemble COVID-19's SARS-CoV-II virus. Several experimental vaccines were developed from SARS and MERS[20]. These viruses and experimental MERS and SARS vaccines laid the groundwork for SARS-CoV-II vaccines. Epitope mapping and targeting SARS-CoV-II spike protein for developing different vaccines against infection were aided by comparisons between SARS-CoV-I and SARS-CoV-II using the NIAID virus pathogen database and analysis resource and the immune epitope database (IEDB) [20,21].

3. SARS-CoV-II VACCINE DEVELOPMENT

Standardized and innovative methods were used for vaccine development. A new paradigm is required to successfully develop a vaccine in a short time, with a lot of effort and money [31]. It is more challenging to conduct clinical trials during a pandemic. However, many clinical trials were needed to determine the safety and efficacy of the vaccine candidates to ensure public acceptance. Conventional vaccine development times can be shortened during epidemics using cutting-edge sequencing and reverse genetics technology. They are necessary to establish a globally equitable vaccine distribution system and determine the population group that continues to be at greater risk when a vaccine becomes available.

3.1. Standard research methods

Good clinical practices and clinical research principles were followed during the entire process of vaccine development. Before the human trials began, local institutional review boards (IRBs), FDA, and other regulatory agencies reviewed study protocols and consent forms. Informed consent and subject rights were protected.

3.2. Trials Size

Clinical trials remained large. Large-scale COVID-19 efficacy and safety studies used 30,000 to 45,000 subjects randomized 1:1 or 2:1 vaccine to placebo to detect statistical differences between vaccine and placebo recipients. The safety and efficacy of other licensed vaccines were demonstrated in clinical trials ranging from 1000 subjects for Varicella and Hepatitis-A vaccines to 70,000 for Rotavirus vaccines to put these studies in perspective [18].

3.3. Concurrent conduction of Clinical Trials

Innovation accelerated clinical trial design and execution following standard procedures. Parallel clinical trials allowed for faster completion. Overlapping phases 1,2 and 3 studies achieved this. Regulators helped to determine what information was needed to advance development. For instance, phase 2 was started after phase 1 safety data was collected to reduce risk. Parallel to phase 1 studies, preclinical animal studies were conducted [31].

3.4. Safety

Safety was monitored in all COVID-19 studies. This includes daily reporting of post-vaccination events for a week and longer follow-up of severe events. An independent data safety monitoring board (DSMB) was created to review safety data in each trial and stop futile studies [16,18].

4. STRATEGIES FOR VACCINE DEVELOPMENT

The development of vaccines across multiple platforms is an essential strategy for dealing with the global spread of coronavirus disease. Under the ACTIV (Accelerating COVID-19 Therapeutic Interventions and Vaccine), a public-private partnership, NIH collaborated with its sister agencies in the Department of Health and Human Services, including the US Food and Drug Administration (US-FDA), Centers for Disease Control and Prevention (CDC), Biomedical Advanced Research and Development Authority (BARD), and other US government departments, such as the Departments of Defense and Veterans Affairs; the European Medicines Agency (EMA); and representatives from academia, philanthropic organizations [30]. This forum facilitated vaccine trial design discussions, data sharing, and public-private collaboration to conduct vaccine efficacy studies quickly.

There is a growing consensus that vaccine trials should use joint independent laboratories or contribute samples and data to generate surrogate markers that speed licensure and efficacy comparison. A joint Institutional Review Board and cross-trial DSMB should coordinate the entire enterprise's regulatory framework and allow regulatory agencies and the public to assess effect sizes between approaches objectively. Phase 3 planning must begin as vaccine candidates enter phase 1.

Vaccines are created using different manufacturing platforms, gene synthesis, protein engineering, computational biology, and structure-based antigen 22. There are several building blocks for COVID-19 vaccine development, such as complete viruses (Inactivated or attenuated), Viral vectors (Replicating), Antigenic subunits (Proteins or peptides), Nucleic acids (RNA or DNA), and virus-like particles. In addition, some crucial aspects are considered while developing the vaccine, such as Vaccine stability, Cellular, and humoral immunogenicity, Manufacturing cost, and speed.

4.1. Viral Vaccines

Viral vaccines use attenuated or inactivated viruses. This strategy may harm immunosuppressed people. Measles and polio vaccines are made this way but require extensive safety testing [18]. Until they acquire pathogenic mutations, attenuated viruses are passed through animals or humans. Formaldehyde and heat inactivate viruses. However, it requires many live viruses.

4.2. Viral Vector-based vaccines

Viral vector-based vaccines introduce SARS-CoV-II genes into hosts. This method boosts immunogenicity without adjuvants and induces a strong cytotoxic T-cell response to kill virus-infected cells. Some vaccines enter cells and produce SARS-CoV-II protein, but essential genes are disabled, so the vector cannot replicate. In other vaccines, the vector replicates slowly with SARS-CoV-II proteins on its surface. These vaccines are safe and induce strong immunity[18, 21,25,31].

4.3. Protein vaccines

This vaccine directly injects coronavirus proteins. Shell fragments and virus-like proteins can also be used. Most vaccines use viral protein subunits, specifically the spike protein. SARS-CoV vaccines that protected monkeys were not tested in humans. These vaccines may need adjuvants, immunostimulants, and multiple doses. Vaccines made from virus-like particles that resemble SARS-CoV-II are not infectious because they lack genetic material. These vaccines have a robust immune response but are hard to make [15,16,18,22,25,31].

4.4. Nucleic acid-based vaccines

SARS-CoV-II nucleic acid is inserted into human cells, which produce virus proteins that stimulate an immune response. Plasmid DNA vaccines efficiently express SARS-CoV-II antigens in host cells. Electroporation opens cell membranes for DNA ab-sorption [16,18,31]. At present, there are no human DNA vaccines approved. mRNA vaccines use liposomes to deliver SARS-CoV-II antigens to host cells. DNA and RNA vaccines are safe and easy to make. The virus genome is enough to make them.

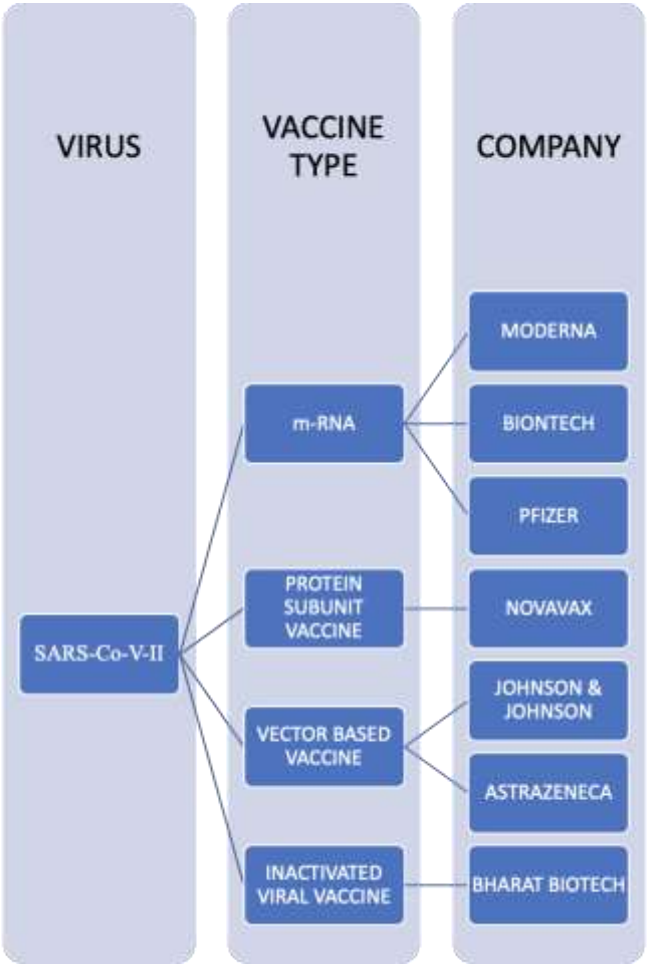

Figure 1- SRAS-CoV-II Vaccine Type and developers

Table 1- Vaccine platform and their potential advantages and disadvantages

Vaccine platform	Advantages	Disadvantages
mRNA	Elicit immune response No risk of genomic integration	Require delivery by lipid Possible inflammatory reaction
Protein Subunit Vaccine	Target key antigens No biosafety concerns	Need adjuvants
Vector Base Vaccine	Precise immune response	Variable immunogenicity Risk of genomic integration
Live attenuated	Long-lasting immune response Do not need adjuvants	Potential risk of disease causes reactogenicity

4.5. Large-Scale Manufacturing of Vaccines

Manufacturing vaccines is difficult and time-consuming because quality control must be consistent. The US and several other governments risked funding the manufacturing of the most promising COVID-19 vaccine candidates to speed up availability[18]. After early clinical results were available, billions of government dollars were invested to allow manufacturers to enhance their biomanufacturing infrastructure and begin vaccine manufacturing, increasing the likelihood of millions of vaccine doses being immediately available after regulatory approval.

5. REGULATORY REQUIREMENTS

Early scientific advisory meetings, US-FDA guidance, and manufacturing measures helped pharmaceutical companies manufacture safe and effective vaccines. In addition, US-FDA Fast-tracked application scientific review for medical conditions that did not meet the criteria, allowing sponsors to get approval to accelerate vaccine development in response to the COVID-19 pandemic (Lynch, 2020). US-FDA gave Emergency Use Authorization (EUA) for the vaccine.

According to Bolislis, 2020, crucial steps were taken to manage the pandemic response. Information collected during the pandemic resulted in 1705 documents regarding the impact of the virus being collected and classified.[28] Out of which 343 were related to regulatory flexibilities. The approaches to gain agility were expediting medical products for use and supply chain issues, building international cooperation, and implementing electronic tools to address regulatory burdens.

The trend below shows the distribution of regulatory documents and demonstrates the accelerated growth of information published in response to the pandemic. The graph is a depiction of trends across the globe. The document reduction shows better efficiency in managing the pandemic response by implementing different approaches.

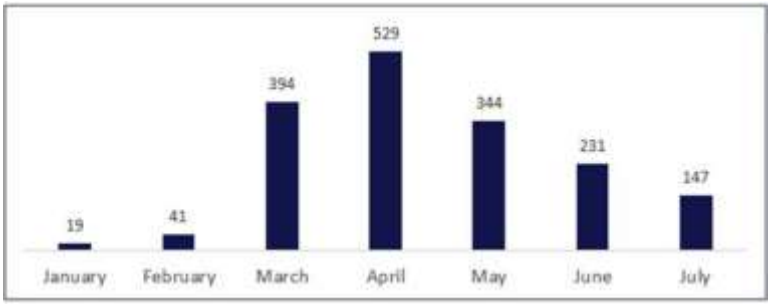

Figure 2- Distribution model of regulatory documents

Note: This model was produced by Bolislis in 2020, trending the growth of regulatory documents from January 2020 to July 2020.[28]

The regulator documents were further classified into the following categories, with most documents related to communications like press releases, announcements, notices, etc. Moreover, the second largest category is pertinent to guidance documents.

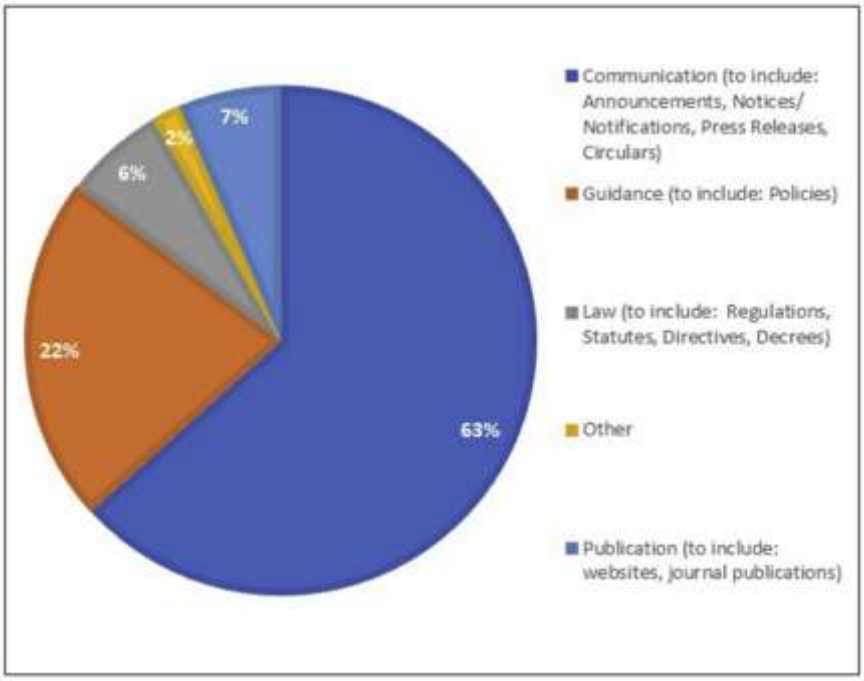

Figure 3 - Type of COVID-19–related documents and information (in percentage).

Note: Bolislis produced this model in 2020, Type of COVID-19–related documents and information (in percentage). Other = documents or information that could not be classified elsewhere (e.g., reports, meeting highlights or summary, or templates). Source: Authors' elaboration, Sanofi COVID-19 regulatory guidance tracker, updated July 31, 2020.

5.1. Mechanism of Regulatory Pliability

According to Lynch et al., 2020 the US FDA and Office for Human Research Protections enforce the regulatory requirements. Still, they have the authority to use discretion to reduce the stringency of certain requirements. Under specific conditions, the US FDA can also waive requirements for investigational new drug and investigational device exemption, including the institutional review board requirements, considering the substitute procedures are ethical. Institutional review boards can exercise interpretive flexibility to add or remove restrictions on requirements.

5.2. Research Evaluation and Approvals

Due to the stress of rapid protocol reviews on the board capacity for the Corona Virus treatment Acceleration Program. This can be expedited through multisite research where academic institutions rely on commercial boards to leverage their research via the Common Rule (Lynch, 2020). The reduction of protocol review per board member can be implemented by dividing it into sub-groups and assigning fewer protocols for review per group.

According to Bolislis, 2020, regulatory authorities have examined expedited pathways to perform a rapid assessment.

Table 2- Pathway for Rapid Assessment

Pathway	Comments
Rapid Scientific Advice	Expedited guidance on test methods, design of research, data collection, and classification
For Review	
Expedited Reviews	To reduce protocol, procedure review, and approval timeline.
Rolling Reviews	Rolling reviews with a 2-week cycle to compile a data packet for marketing authorization with a reduced review timeline.
For Approvals	
Conditional Approvals	If the benefit is greater than the risk, fewer data can be accepted for conditional marketing authorization, which is valid for one year.
Emergency Use	If no alternative is present, medical devices can be approved.
Expanded Access	Use of products under investigation for life-threatening conditions
Special Programs	
Coronavirus Treatment Acceleration Program (CTAP)	An emergency program for the discovery and development of new COVID-19 treatments
Operation Warp Speed (OWS)	Accelerating distribution and production of vaccines.

5.3. Informed Consent

According to Lynch 2020, the US FDA recommended electronic consent by video and phone conferencing using the MyStudies Application due to the physical distancing requirements implemented during the pandemic.[27] Before initiating the study, consent by the patient or legal representative is required; alternative methods can be used. As consent is an ongoing practice, patients should be informed of any new development risk associated with positive or negative outcomes to help them decide. According to the US FDA, the research data should be managed by CTAP (Corona Virus treatment Acceleration Program) instead of IRB to avoid work duplication and maintain data integrity.

5.4. Emergency Consent

In an emergency, exceptions from informed consent can be exercised under life-threatening. The roadblock, in this case, is that Institutional Review Boards are required to consult with individuals from the community group to rapidly select eligible subjects for research. This practice for emergency consent takes a long time and can hinder the research timeline. IRBs can identify high-risk communities, consult with community advocates or people in a position of influence, and use remote consultation methods to expedite the selection process.

5.5. Adherence to Regulations & Representation

According to Stephen 2021, adherence to regulations implemented by the authorities has remained greater than 90% despite the human condition and frailties. Due to the availability effect, violation of regulations is remembered more easily than adherence leading to a biased view of the severity and classification of the violation resulting in people not following rules because they think other people are not following them as well. The reporting of stories of non-adherence may have led to increased violations, whereas stories that highlight effort and resilience may have been a better narrative.

5.6. Regulatory Filing strategy

US FDA fast-tracked approval for emergency use of the vaccine. At the same time, Conditional Rapid Vaccine approval by EMA was provided. US FDA and EMA approvals were used as a reference for worldwide regulatory submissions. Marketing approval to independent market for Vaccine marketing application submissions and approval were prioritized. All vaccine manufacturing quality standards and large-scale commercialization standards were met during the up-scaling of the vaccine. Continuous monitoring of the vaccine is performed by safety surveillance and benefit-risk assessment reporting and by Rapid coordinated regulatory action.

6. CONCLUSION

Over the last several decades, healthcare systems worldwide have accumulated a wealth of data, experience, and understanding regarding vaccine research, deployment, and monitoring. Vaccines development efforts for the public health threats posed by the COVID-19 pandemic benefited greatly

from lessons learned from previous vaccine development, evaluation, approval, and surveillance program. An effort was made to collect and organize all the information that could be found on COVID-19 disease from various resources and published works to save the valuable reader time. This review article performed a review of multiple articles and papers to understand strategies for COVID-19 vaccine development methods, the regulatory requirements, and vaccine approval methods used by different agencies. The review has extensively discussed the history of COVID-19, possible routes of SARS-CoV-II invasion, virus variants, implications on the health, vaccine development, vaccine types, details on the pros and cons of available curatives (vaccines) across the globe, and their regulatory requirement.

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