RESEARCH PAPER

COVID-19 Vaccine Development: A Critical Review of Accelerated Preclinical and Clinical Evaluation, Regulatory Pathways, and Pharmacological Perspectives

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ABSTRACT

The Coronavirus Disease 2019 (COVID-19) pandemic posed an unprecedented global public health crisis, necessitating the rapid development of safe and effective vaccines to mitigate widespread morbidity, mortality, and socioeconomic disruption. Traditionally, vaccine development is a lengthy process spanning 10–15 years and involves sequential stages of exploratory research, preclinical investigations, phased clinical trials, regulatory review, large-scale manufacturing, and post-marketing surveillance. In contrast, multiple COVID-19 vaccines received Emergency Use Authorization (EUA) or conditional approval within approximately one year, raising important scientific and regulatory questions regarding the accelerated development pathway. This review critically examines the complete vaccine development continuum, with particular emphasis on the transition from conventional to accelerated approaches adopted during the COVID-19 pandemic. The review synthesizes evidence on preclinical evaluation, clinical trial design, vaccine platforms, pharmacological mechanisms, regulatory innovations, manufacturing strategies, and pharmacovigilance systems. Furthermore, it compares traditional vaccine development timelines with pandemic-specific accelerated strategies, including overlapping clinical phases, rolling regulatory reviews, manufacturing at financial risk, and extensive global collaboration. Particular attention is given to the pharmacological principles underlying immune response, vaccine efficacy, dose optimization, safety assessment, and long-term surveillance. The available evidence indicates that the accelerated development of COVID-19 vaccines was primarily facilitated by prior coronavirus research, unprecedented financial investment, international scientific collaboration, adaptive clinical trial methodologies, and expedited regulatory procedures rather than the omission of essential scientific evaluation. Preclinical studies, Phase I–III clinical trials, and continuous post-marketing safety monitoring remained integral components of vaccine assessment. Lessons learned from the COVID-19 vaccine development experience provide valuable insights for future pandemic preparedness, regulatory flexibility, and the advancement of next-generation vaccine technologies. This review highlights how scientific innovation and evidence-based regulatory practices can substantially reduce vaccine development timelines while maintaining rigorous standards of quality, safety, and efficacy.

Keywords: COVID-19; SARS-CoV-2; Vaccine Development; Preclinical Studies; Clinical Trials; Accelerated Development; Pharmacology; Immunopharmacology; Regulatory Science; Emergency Use Authorization; Pharmacovigilance; Vaccine Safety.

How to cite this article: Khan F, Sisodia S. S. COVID-19 Vaccine Development: A Critical Review of Accelerated Preclinical and Clinical Evaluation, Regulatory Pathways, and Pharmacological Perspectives. Int J Drug Deliv Technol. 2026;16(74s): 2161-2177. DOI: 10.25258/ijddt.16.74s.179

Source of support: Nil

Conflict of interest: None

1. INTRODUCTION

Vaccination has long been recognized as one of the most effective public health interventions, significantly reducing the global burden of infectious diseases and preventing millions of deaths each year. Since Edward Jenner introduced the first smallpox vaccine in 1796, continuous advances in immunology, microbiology, molecular biology, and pharmaceutical sciences have transformed vaccine development into a highly sophisticated and evidence-based process. Vaccines have successfully controlled or eradicated several life-threatening diseases, including smallpox, poliomyelitis, measles, hepatitis B, and human papillomavirus (HPV)-associated infections, highlighting their critical role in improving global health and increasing life expectancy.[1][2]

The emergence of Coronavirus Disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), created an unprecedented global health emergency. Following its identification in Wuhan, China, in December 2019, the virus spread rapidly across the world due to its high transmissibility. On 30 January 2020, the World Health Organization (WHO) declared COVID-19 a Public Health Emergency of International Concern, and on 11 March 2020, it was officially characterized as a pandemic. The rapid increase in infections, hospitalizations, and mortality overwhelmed healthcare systems while causing severe economic disruption and social instability worldwide. Although public health measures such as lockdowns, mask mandates, physical distancing, and travel restrictions temporarily reduced viral transmission, these interventions alone were insufficient to control the pandemic. Consequently, the rapid development of safe and effective vaccines became a global scientific priority.[3][4]

Traditionally, vaccine development is a lengthy, sequential, and highly regulated process that typically requires 10–15 years before a vaccine receives marketing approval. The conventional pathway includes exploratory research, antigen identification, preclinical studies, Phase I–III clinical trials, regulatory review, manufacturing, and post-marketing surveillance. Each stage is designed to ensure that vaccines demonstrate acceptable levels of safety, immunogenicity, efficacy, and manufacturing quality before being administered to healthy populations. Because vaccines are preventive interventions, regulatory agencies maintain particularly stringent standards for their evaluation.[5][6][7]

The COVID-19 pandemic dramatically altered the pace of vaccine development. Within approximately one year of the publication of the SARS-CoV-2 genome sequence, several vaccine candidates successfully completed clinical trials and received Emergency Use Authorization (EUA) or conditional approval. This unprecedented achievement generated considerable scientific interest and public debate regarding how such rapid development was possible. Contrary to common misconceptions, the accelerated timeline was not achieved by eliminating essential stages of vaccine evaluation. Instead, it resulted from the convergence of decades of coronavirus research, innovative vaccine platform technologies, unprecedented financial investment, international scientific collaboration, adaptive clinical trial designs, manufacturing at financial risk, and rolling regulatory review by global health authorities. These strategies allowed several development activities to occur simultaneously while maintaining the fundamental scientific principles governing vaccine safety, efficacy, and quality.[8][9][10][11]

From a pharmacological perspective, COVID-19 vaccines introduced significant advancements in immunopharmacology through the successful application of messenger RNA (mRNA), viral vector, protein subunit, and inactivated vaccine platforms. These technologies stimulate both humoral and cell-mediated immune responses by presenting the SARS-CoV-2 spike protein to the immune system through different mechanisms. Their widespread implementation also emphasized the importance of post-marketing pharmacovigilance, as continuous safety monitoring became essential for identifying rare adverse events and evaluating long-term vaccine effectiveness in diverse populations.[12][13]

The rapid development and global deployment of COVID-19 vaccines have transformed conventional concepts of vaccine research, regulatory science, and pandemic preparedness. The experience demonstrated that scientific innovation, coordinated international collaboration, and adaptive regulatory frameworks can substantially shorten vaccine development timelines without compromising evidence-based evaluation. At the same time, it highlighted the importance of transparency, public confidence, equitable vaccine access, and robust pharmacovigilance systems.[14][15][16]

This review critically examines the complete development pathway of COVID-19 vaccines, with particular emphasis on traditional vaccine development, preclinical evaluation, clinical trials, accelerated regulatory strategies, pharmacological mechanisms, and post-marketing safety surveillance. Furthermore, it compares conventional and accelerated vaccine development approaches to identify the scientific innovations and regulatory adaptations that enabled the rapid availability of COVID-19 vaccines while maintaining internationally accepted standards of quality, safety, and efficacy.[17][18]

2. TRADITIONAL VACCINE DEVELOPMENT PROCESS

The development of a vaccine is a rigorous, evidence-based, and highly regulated process designed to ensure that a vaccine is safe, effective, and of consistent quality before it is introduced into public immunization programs. Unlike therapeutic drugs, which are administered to patients with an existing disease, vaccines are primarily given to healthy individuals to prevent future infections. Consequently, regulatory agencies such as the World Health Organization (WHO), the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and national regulatory authorities require extensive scientific evidence demonstrating a favourable benefit–risk profile prior to approval. Under conventional circumstances, vaccine development generally requires 10–15 years, progressing through sequential stages of research, preclinical evaluation, clinical testing, regulatory review, manufacturing, and post-marketing surveillance.[19][20]

2.1 Exploratory Research and Antigen Discovery

The first stage of vaccine development involves identifying suitable antigenic targets capable of inducing protective immune responses. Researchers investigate the pathogen's genetic structure, virulence factors, mechanisms of infection, and host–pathogen interactions to determine the most appropriate vaccine candidate. Advances in genomics, proteomics, structural biology, and bioinformatics have significantly improved the identification of immunogenic antigens and accelerated the design of vaccine candidates. During this stage, scientists also evaluate different vaccine platforms, including live attenuated, inactivated, protein subunit, viral vector, and nucleic acid-based vaccines, to determine the most effective strategy for antigen delivery.[21][22]

2.2 Preclinical Evaluation

Following antigen selection, vaccine candidates undergo extensive preclinical testing to evaluate their biological activity, immunogenicity, and preliminary safety before administration to humans. Preclinical studies consist of both in vitro laboratory investigations and in vivo animal experiments conducted under Good Laboratory Practice (GLP) guidelines.[23]

In vitro studies examine antigen expression, formulation stability, immune activation, and cellular responses using cultured cell lines and molecular assays. These investigations provide initial evidence regarding the vaccine's ability to stimulate immune pathways and generate antigen-specific responses.[24]

Subsequently, vaccine candidates are evaluated in animal models such as mice, hamsters, ferrets, rabbits, or non-human primates, depending on the characteristics of the target disease. Animal studies assess acute and chronic toxicity, local and systemic reactogenicity, immunogenicity, dose optimization, route of administration, and protective efficacy following pathogen challenge. Only vaccine candidates demonstrating acceptable safety profiles and sufficient immune protection are considered suitable for clinical evaluation.[25]

2.3 Clinical Development

Clinical development represents the most resource-intensive phase of vaccine research and is conducted according to Good Clinical Practice (GCP) guidelines after approval by regulatory authorities and institutional ethics committees. Clinical evaluation is performed sequentially through Phase I, Phase II, and Phase III trials, each designed to answer specific scientific and regulatory questions.[19][20]

Phase I clinical trials generally enrol 20–100 healthy adult volunteers and primarily evaluate vaccine safety, tolerability, reactogenicity, and preliminary immunogenicity. Dose-escalation studies are commonly performed to identify the optimal dosage while monitoring participants for immediate adverse events.[26]

Phase II clinical trials involve several hundred participants and further assess vaccine safety while optimizing dosage schedules, formulation, and immunogenicity. These randomized controlled studies provide valuable information regarding antibody production, cellular immune responses, and vaccination schedules across different population groups.[26]

Phase III clinical trials are large, multicentre, randomized studies involving thousands to tens of thousands of participants. Their primary objective is to demonstrate vaccine efficacy in preventing disease while simultaneously identifying less common adverse events that may not be detected during earlier phases. The results of Phase III trials form the principal scientific evidence supporting regulatory approval.[26]

2.4 Regulatory Review and Manufacturing

Following successful clinical development, manufacturers submit a comprehensive regulatory dossier containing data from preclinical studies, clinical trials, manufacturing processes, quality control, and risk management plans. Regulatory agencies conduct an independent scientific assessment to determine whether the available evidence demonstrates acceptable standards of quality, safety, and efficacy.[9][10]

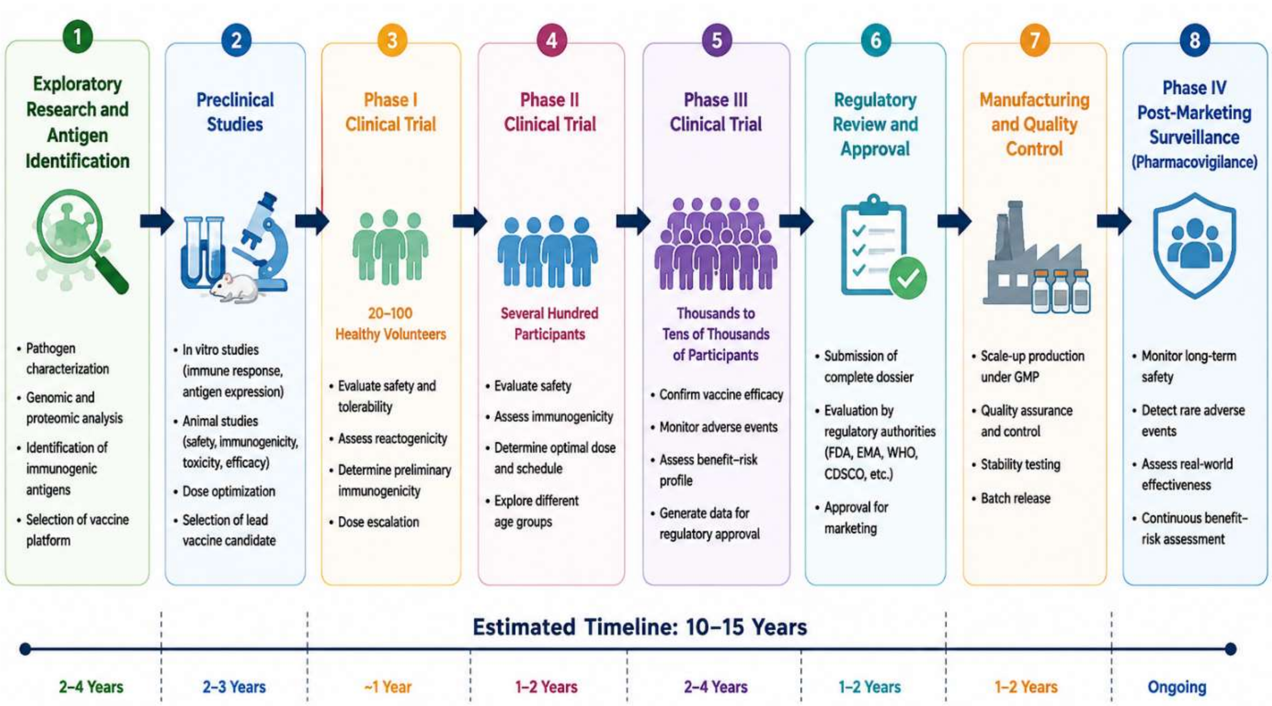
Once regulatory approval is obtained, vaccine production is performed under Good Manufacturing Practice (GMP) standards to ensure batch-to-batch consistency, sterility, purity, potency, and product stability. Continuous quality assurance and quality control testing are implemented throughout manufacturing to maintain compliance with international regulatory requirements.[19][20]

2.5 Post-Marketing Surveillance (Phase IV)

The evaluation of a vaccine continues after regulatory approval through Phase IV studies and pharmacovigilance programs. Since rare adverse events may only become apparent after millions of individuals have been vaccinated, continuous safety monitoring is essential for maintaining public confidence and ensuring long-term vaccine safety.[27]

Post-marketing surveillance systems collect real-world data on adverse events, vaccine effectiveness, duration of protection, and performance in special populations, including older adults, pregnant women, and immunocompromised individuals. National and international pharmacovigilance programs, including spontaneous reporting systems and active surveillance networks, support ongoing benefit–risk assessments and enable regulatory authorities to modify vaccination recommendations when necessary.[18]

Figure 1: Sequential steps in traditional vaccine development pathway



3. COVID-19 VACCINE DEVELOPMENT

The emergence of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in December 2019 triggered an unprecedented global effort to develop vaccines capable of controlling the rapidly spreading COVID-19 pandemic. Unlike previous vaccine development programs, which often required more than a decade to progress from laboratory research to regulatory approval, the urgent public health crisis demanded an accelerated yet scientifically rigorous approach. Within one year of the publication of the viral genome, multiple COVID-19 vaccines had successfully completed clinical evaluation and received Emergency Use Authorization (EUA) or conditional approval, representing one of the most remarkable achievements in modern pharmaceutical and biomedical research.[8][9][10][11][19][20]

A major factor contributing to this rapid progress was the availability of prior scientific knowledge regarding coronaviruses. Previous outbreaks of severe acute respiratory syndrome (SARS) in 2002–2003 and Middle East Respiratory Syndrome (MERS) in 2012 had stimulated extensive research on coronavirus biology, pathogenesis, and immune responses. These investigations identified the spike (S) glycoprotein as the primary antigen responsible for viral entry into host cells through interaction with the angiotensin-converting enzyme 2 (ACE2) receptor. Since neutralizing antibodies directed against the spike protein were shown to provide protective immunity, this protein became the principal target for nearly all COVID-19 vaccine candidates.[1][3][8]

The publication of the complete SARS-CoV-2 genome sequence in January 2020 enabled researchers worldwide to initiate vaccine design immediately. Advances in genomic sequencing, structural biology, bioinformatics, and reverse vaccinology significantly accelerated antigen identification and vaccine optimization. Simultaneously, unprecedented international collaboration among academic institutions, biotechnology companies, pharmaceutical industries, governments, and global health organizations facilitated rapid sharing of scientific data, research infrastructure, and financial resources. Programs such as the Coalition for Epidemic Preparedness Innovations (CEPI), Operation Warp Speed, and the Access to COVID-19 Tools (ACT) Accelerator played crucial roles in supporting vaccine research, manufacturing capacity, and equitable global distribution.[8][9]

Unlike conventional vaccine development, COVID-19 vaccines were developed using multiple technological platforms simultaneously. This diversified strategy increased the probability of identifying safe and effective vaccine candidates while allowing different manufacturing approaches to meet global demand.[12][13]

3.1 Major COVID-19 Vaccine Platforms

Messenger RNA (mRNA) Vaccines

Messenger RNA vaccines represented the first successful large-scale application of mRNA technology in human vaccination. These vaccines deliver synthetic mRNA encoding the SARS-CoV-2 spike protein within lipid nanoparticles. Following intramuscular administration, host cells translate the mRNA into viral spike protein, which subsequently stimulates both humoral and cellular immune responses. The major advantages of mRNA vaccines include rapid design, flexible manufacturing, and strong immunogenicity; however, they require stringent cold-chain storage conditions due to the instability of RNA molecules.[8][10][12]

Examples: Pfizer–BioNTech (BNT162b2) and Moderna (mRNA-1273).

Viral Vector Vaccines

Viral vector vaccines employ replication-deficient adenoviruses engineered to carry the gene encoding the SARS-CoV-2 spike protein. After entering host cells, the viral vector delivers genetic material that directs spike protein synthesis, inducing robust antibody and T-cell responses. These vaccines offer greater storage stability than mRNA vaccines but may exhibit reduced immunogenicity in individuals with pre-existing immunity to the viral vector.[4][6][13]

Examples: Oxford–AstraZeneca (ChAdOx1 nCoV-19), Johnson & Johnson (Ad26.COV2.S), and Sputnik V.

Inactivated Whole-Virus Vaccines

Inactivated vaccines are produced by chemically inactivating SARS-CoV-2 while preserving its antigenic structure. Because the virus is incapable of replication, these vaccines have an established safety profile and can be manufactured using conventional vaccine production technologies. However, they often require adjuvants and booster doses to achieve optimal immune responses.[5][14][15]

Examples: Covaxin (BBV152), CoronaVac (Sinovac), and BBIBP-CorV (Sinopharm).

Protein Subunit Vaccines

Protein subunit vaccines contain purified recombinant spike proteins or receptor-binding domain (RBD) antigens formulated with immunological adjuvants to enhance immune responses. These vaccines exhibit excellent safety profiles but generally require multiple doses to induce durable immunity.[5][14][15]

Example: Novavax (NVX-CoV2373).

DNA Vaccines

DNA vaccines utilize plasmid DNA encoding the spike protein, allowing host cells to synthesize viral antigens and stimulate adaptive immunity. Although DNA vaccines demonstrate excellent stability and relatively simple storage requirements, their global use during the COVID-19 pandemic remained limited.[16][17]

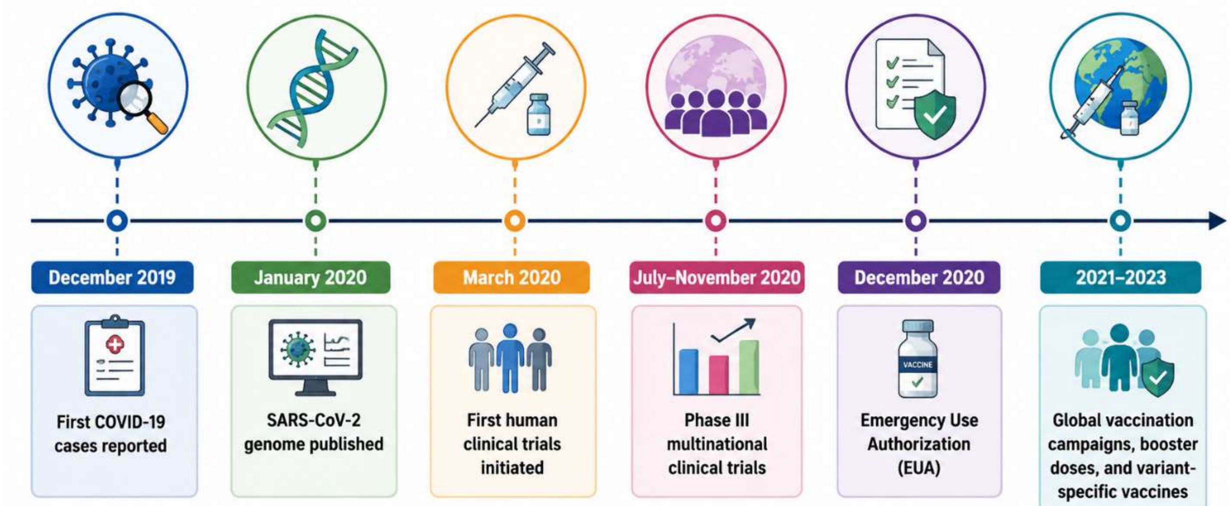
Example: ZyCoV-D.

3.2 Clinical Progress and Global Deployment

Following successful preclinical studies, multiple vaccine candidates rapidly entered Phase I, II, and III clinical trials involving tens of thousands of participants across different countries. Large multicentre randomized controlled trials demonstrated high levels of efficacy in preventing symptomatic COVID-19, severe disease, hospitalization, and mortality. Following regulatory authorization, mass vaccination campaigns were initiated worldwide, resulting in billions of administered doses and substantial reductions in COVID-19-related morbidity and mortality.[11][12]

Despite the remarkable success of vaccination programs, continuous surveillance remained necessary because of the emergence of new viral variants, waning immunity, and rare adverse events. Consequently, booster vaccination strategies, variant-adapted vaccines, and ongoing pharmacovigilance became integral components of the global vaccination program.[18][27]

Figure 2: COVID-19 vaccine development timeline



4. ACCELERATED COVID-19 VACCINE DEVELOPMENT: SCIENTIFIC AND REGULATORY INNOVATIONS

The rapid development of COVID-19 vaccines represents an unprecedented achievement in modern pharmaceutical science and public health. Traditionally, vaccine development requires 10–15 years to progress through exploratory research, preclinical testing, phased clinical trials, regulatory evaluation, manufacturing, and post-marketing surveillance. In contrast, the first COVID-19 vaccines received Emergency Use Authorization (EUA) within approximately 11 months after the publication of the SARS-CoV-2 genome. This remarkable achievement raised concerns regarding whether scientific standards had been compromised. However, accumulating evidence demonstrates that the accelerated timeline resulted primarily from scientific preparedness, technological innovation, regulatory flexibility, and global collaboration rather than the omission of essential stages of vaccine evaluation.[8][9][10][11]

One of the most significant contributors to accelerated vaccine development was the extensive body of knowledge generated from previous coronavirus outbreaks. Research conducted during the SARS (2002–2003) and MERS (2012) epidemics had already identified the spike (S) glycoprotein as the principal target for neutralizing antibodies and protective immunity. Consequently, once the complete SARS-CoV-2 genome sequence became publicly available in January 2020, researchers were able to rapidly design vaccine candidates without repeating years of exploratory antigen discovery. Furthermore, advances in structural biology, computational modelling, and reverse vaccinology enabled rapid optimization of vaccine constructs while maintaining scientific rigor.[10][11]

Another major innovation involved the use of platform technologies that had been under development for many years before the COVID-19 pandemic. Messenger RNA (mRNA), viral vector, protein subunit, and DNA vaccine platforms had previously undergone extensive laboratory and early clinical evaluation for diseases such as influenza, Ebola, Zika virus infection, and Middle East Respiratory Syndrome. Instead of creating entirely new vaccine manufacturing systems, developers adapted these established platforms by incorporating the genetic sequence encoding the SARS-CoV-2 spike protein. This strategy significantly reduced development time while preserving established manufacturing and quality-control procedures.[12][13]

Unlike the conventional sequential model of vaccine development, COVID-19 vaccine programs adopted parallel development strategies. Traditionally, each phase of development begins only after successful completion of the previous phase. During the pandemic, several activities—including process development, manufacturing scale-up, and clinical trial preparation—were performed simultaneously. Importantly, clinical trials continued to follow the established Phase I, Phase II, and Phase III framework; however, transitions between phases occurred immediately after predefined safety and immunogenicity criteria were met. This overlapping approach eliminated administrative delays while maintaining continuous scientific evaluation.[8][9]

Large-scale financial investment also played a crucial role in accelerating vaccine availability. Vaccine development is generally associated with substantial financial risk because manufacturers invest considerable resources without assurance of regulatory approval. During the COVID-19 pandemic, governments, international organizations, and private industries provided unprecedented funding through initiatives such as

Operation Warp Speed, the Coalition for Epidemic Preparedness Innovations (CEPI), and the Access to COVID-19 Tools (ACT) Accelerator. These investments supported research, clinical trials, manufacturing infrastructure, and advance purchase agreements, enabling companies to expand production capacity before receiving regulatory approval. This strategy, commonly known as manufacturing at risk, substantially shortened the interval between authorization and vaccine distribution while shifting financial rather than scientific risk.[10][11]

Clinical trial implementation was also accelerated because of the widespread transmission of SARS-CoV-2. Conventional vaccine trials often require several years to recruit participants and accumulate sufficient disease endpoints for efficacy analysis. During the COVID-19 pandemic, the high incidence of infection allowed investigators to rapidly enrol tens of thousands of participants across multiple countries and evaluate vaccine efficacy within months. The resulting Phase III trials were among the largest vaccine studies ever conducted and provided robust evidence regarding vaccine safety, efficacy, and protection against severe disease.[23][24]

Regulatory authorities introduced several procedural innovations while maintaining internationally accepted standards for vaccine evaluation. One of the most important adaptations was the implementation of rolling review, whereby regulatory agencies evaluated preclinical, manufacturing, and clinical data as they became available rather than waiting for a complete submission at the end of development. This continuous review process enabled agencies such as the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), the Medicines and Healthcare products Regulatory Agency (MHRA), and other national authorities to identify deficiencies promptly, request additional information when necessary, and complete final assessments more efficiently.[9][10]

Emergency Use Authorization (EUA) represented another important regulatory mechanism adopted during the pandemic. EUA allows temporary authorization of medical products during public health emergencies when the available evidence indicates that the potential benefits outweigh the known and potential risks, and when no adequate approved alternatives are available. It is important to distinguish EUA from full licensure; emergency authorization does not eliminate requirements for safety and efficacy evaluation but permits earlier public access while additional clinical and post-marketing data continue to be collected.[9][10]

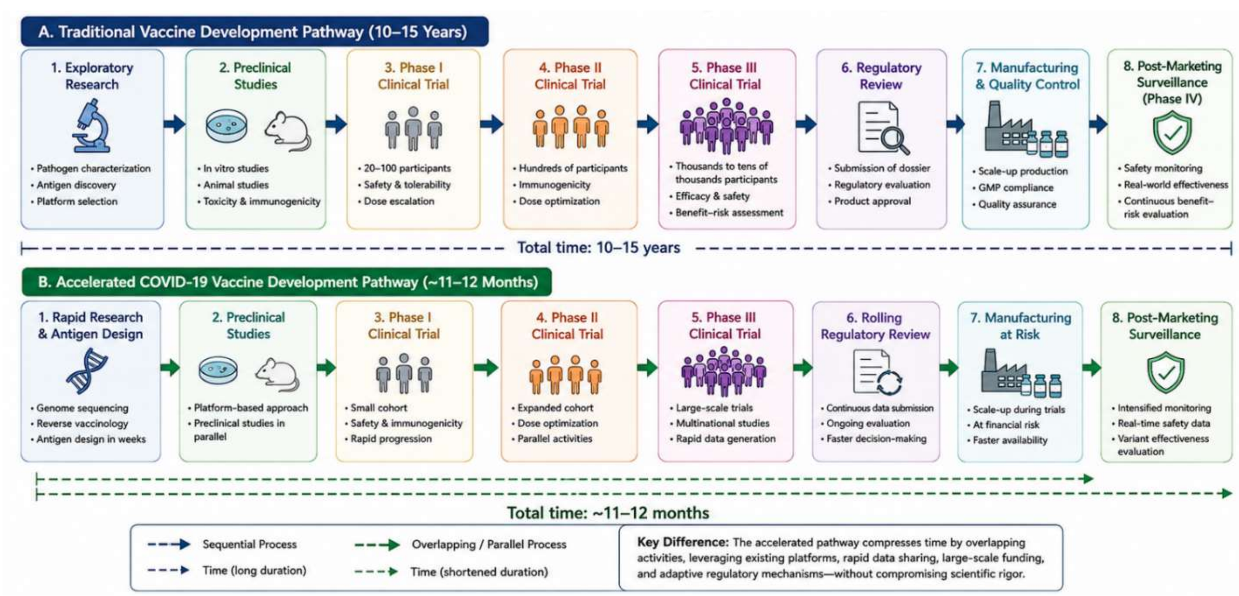
Continuous pharmacovigilance constituted another essential component of the accelerated development pathway. Although large Phase III trials enrolled tens of thousands of participants, rare adverse events may only become apparent after millions of individuals have been vaccinated. Consequently, extensive post-marketing surveillance systems—including VAERS (United States), EudraVigilance (European Union), the Yellow Card Scheme (United Kingdom), and other national pharmacovigilance programs—monitored vaccine safety in real time. These systems enabled rapid detection and investigation of rare adverse events, assessment of vaccine effectiveness against emerging viral variants, and evidence-based updates to vaccination recommendations.[18][27]

Overall, the COVID-19 vaccine development program demonstrated that substantial reductions in development timelines can be achieved through scientific preparedness, international collaboration, innovative platform technologies, adaptive clinical trial designs, robust financial investment, and regulatory flexibility. Importantly, the essential components of vaccine evaluation—including preclinical studies, phased clinical trials, manufacturing quality assurance, regulatory oversight, and post-marketing pharmacovigilance—remained integral to the development process. The pandemic therefore established a new paradigm for responding to future global health emergencies while reinforcing the importance of maintaining scientific integrity and public trust.[18][27]

Table 1: Comparison of traditional and accelerated COVID-19 vaccine development

Development Stage	Traditional Vaccine Development	COVID-19 Accelerated Development
Development timeline	10–15 years	~11–12 months
Research approach	Sequential	Parallel and overlapping
Antigen identification	Several years	Weeks after genome sequencing
Preclinical studies	Completed before clinical trials	Completed before human trials; supported by prior platform research
Clinical trials	Sequential Phase I–III	Same phases with rapid transition after predefined milestones
Manufacturing	Begins after approval	Manufacturing at financial risk before approval
Regulatory review	Submission after all data generated	Rolling review of data as generated
Approval pathway	Standard licensure	Emergency Use Authorization (EUA) or conditional approval
Post-marketing surveillance	Routine Phase IV	Intensive real-time pharmacovigilance

Figure 3: Comparison between traditional and accelerated COVID-19 vaccine development pathways



5. PHARMACOLOGICAL PERSPECTIVE OF COVID-19 VACCINES

The unprecedented development and deployment of COVID-19 vaccines have significantly advanced the field of immunopharmacology by introducing novel vaccine platforms capable of inducing robust and long-lasting immune responses. Unlike conventional therapeutic agents that directly target disease-causing mechanisms, vaccines function by stimulating the host immune system to recognize and eliminate pathogens before clinical disease develops. The pharmacological principles underlying COVID-19 vaccines involve antigen delivery, immune activation, generation of immunological memory, and sustained protection against SARS-CoV-2 infection. Understanding these mechanisms is essential for evaluating vaccine efficacy, safety, dosing strategies, and long-term clinical outcomes.[13][14][21][22][23]

5.1 Mechanism of Immune Response

Following intramuscular administration, COVID-19 vaccines introduce viral antigens or genetic material encoding the SARS-CoV-2 spike (S) protein into host cells. Antigen-presenting cells (APCs), particularly dendritic cells and macrophages, internalize these antigens and process them for presentation through the major histocompatibility complex (MHC). This process activates both $CD4^+$ helper T lymphocytes and $CD8^+$ cytotoxic T lymphocytes, initiating adaptive immune responses.[14][21][22][23]

Activated $CD4^+$ T cells stimulate B lymphocytes to differentiate into plasma cells, which produce high-affinity neutralizing antibodies against the spike protein. These antibodies prevent viral attachment to the angiotensin-converting enzyme 2 (ACE2) receptor, thereby inhibiting viral entry into host cells. Simultaneously, activated $CD8^+$ T cells recognize and eliminate infected cells, limiting viral replication and reducing disease severity. Following the primary immune response, memory B cells and memory T cells are generated, enabling rapid and effective immune responses upon future exposure to SARS-CoV-2.[14][21][22][23]

5.2 Pharmacodynamics of COVID-19 Vaccines

The pharmacodynamic effects of COVID-19 vaccines are determined by their ability to induce protective immunity through different antigen delivery systems. Although vaccine platforms differ in design, they share the common objective of stimulating both humoral and cell-mediated immune responses.[13][22][24]

<u>mRNA vaccines</u> (Pfizer-BioNTech and Moderna) deliver lipid nanoparticle-encapsulated messenger RNA encoding the spike protein. Once inside host cells, the mRNA is translated into spike protein, which subsequently activates adaptive immunity without entering the cell nucleus or altering the host genome.[13][22][24]

<u>Viral vector vaccines</u> (Oxford-AstraZeneca, Johnson & Johnson, and Sputnik V) utilize replication-deficient adenoviruses to transport DNA encoding the spike protein into host cells. Following transcription and translation, spike protein expression induces antigen-specific immune responses.[13][15]

<u>Inactivated vaccines</u> (Covaxin, CoronaVac, and Sinopharm) contain chemically inactivated whole SARS-CoV-2 viruses incapable of replication. These vaccines expose the immune system to multiple viral antigens and frequently require adjuvants to enhance immunogenicity.[13][14][21]

<u>Protein subunit vaccines</u>, such as Novavax, contain purified recombinant spike proteins combined with immunostimulatory adjuvants that enhance antigen presentation and antibody production.[16][17]

Despite differences in antigen delivery, all vaccine platforms ultimately generate neutralizing antibodies, activate T-cell immunity, and establish immunological memory capable of reducing severe disease, hospitalization, and mortality.[13][14][21]

5.3 Pharmacokinetic Considerations

Unlike conventional pharmaceuticals, vaccines are not intended to produce systemic pharmacological concentrations. Instead, their biological activity depends on localized antigen expression and immune activation.

Following intramuscular administration, vaccine components remain primarily at the injection site and nearby draining lymph nodes, where antigen presentation occurs. mRNA molecules delivered by lipid nanoparticles are translated intracellularly and rapidly degraded through normal cellular metabolic pathways. Viral vectors infect host cells transiently without replication, while protein subunit and inactivated vaccines undergo antigen processing by immune cells before clearance. Consequently, the protective effect of vaccination depends not on prolonged systemic exposure but on the establishment of durable immunological memory.[21][24][25]

5.4 Dose Optimization and Booster Vaccination

Determining the optimal vaccination schedule is a critical pharmacological consideration. During clinical development, multiple dose levels and dosing intervals were evaluated to maximize immune responses while minimizing adverse reactions. Most COVID-19 vaccines employ a two-dose primary series followed by booster doses to maintain protective immunity.

Booster vaccination enhances neutralizing antibody concentrations, strengthens cellular immune responses, and improves protection against emerging SARS-CoV-2 variants. Heterologous ("mix-and-match") booster strategies have also demonstrated promising immunogenicity, suggesting that combining different vaccine platforms may further broaden immune protection.[3][4][5][6][7]

5.5 Role of Adjuvants

Adjuvants are pharmacologically active components added to certain vaccines to enhance immune responses by stimulating innate immunity and improving antigen presentation. Traditional adjuvants, including aluminium hydroxide and aluminium phosphate, have been widely used in inactivated and protein subunit vaccines to increase antibody production and reduce the amount of antigen required.

Some newer vaccines incorporate advanced adjuvant systems such as Matrix-M, a saponin-based adjuvant used in the Novavax vaccine, which enhances both humoral and cellular immune responses. In contrast, mRNA vaccines do not require conventional adjuvants because the lipid nanoparticle delivery system itself possesses intrinsic immunostimulatory properties.[15][17][24]

5.6 Vaccine–Drug Interactions and Special Populations

Although COVID-19 vaccines demonstrate favourable safety profiles, certain medications may influence vaccine-induced immune responses. Immunosuppressive agents, including corticosteroids, calcineurin inhibitors, biologic therapies, and chemotherapy, can reduce antibody production and cellular immunity, potentially decreasing vaccine effectiveness. Therefore, vaccination timing should be carefully considered in patients receiving immunosuppressive treatment.

Clinical studies have also evaluated vaccine performance in older adults, pregnant women, children, and immunocompromised individuals. Although immune responses may vary among these populations, vaccination remains strongly recommended because the benefits of preventing severe COVID-19 substantially outweigh potential risks. Continuous pharmacovigilance and real-world evidence continue to refine vaccination recommendations for these special populations.[15][18][22]

Figure 4: Mechanism of immune response following COVID-19 vaccination

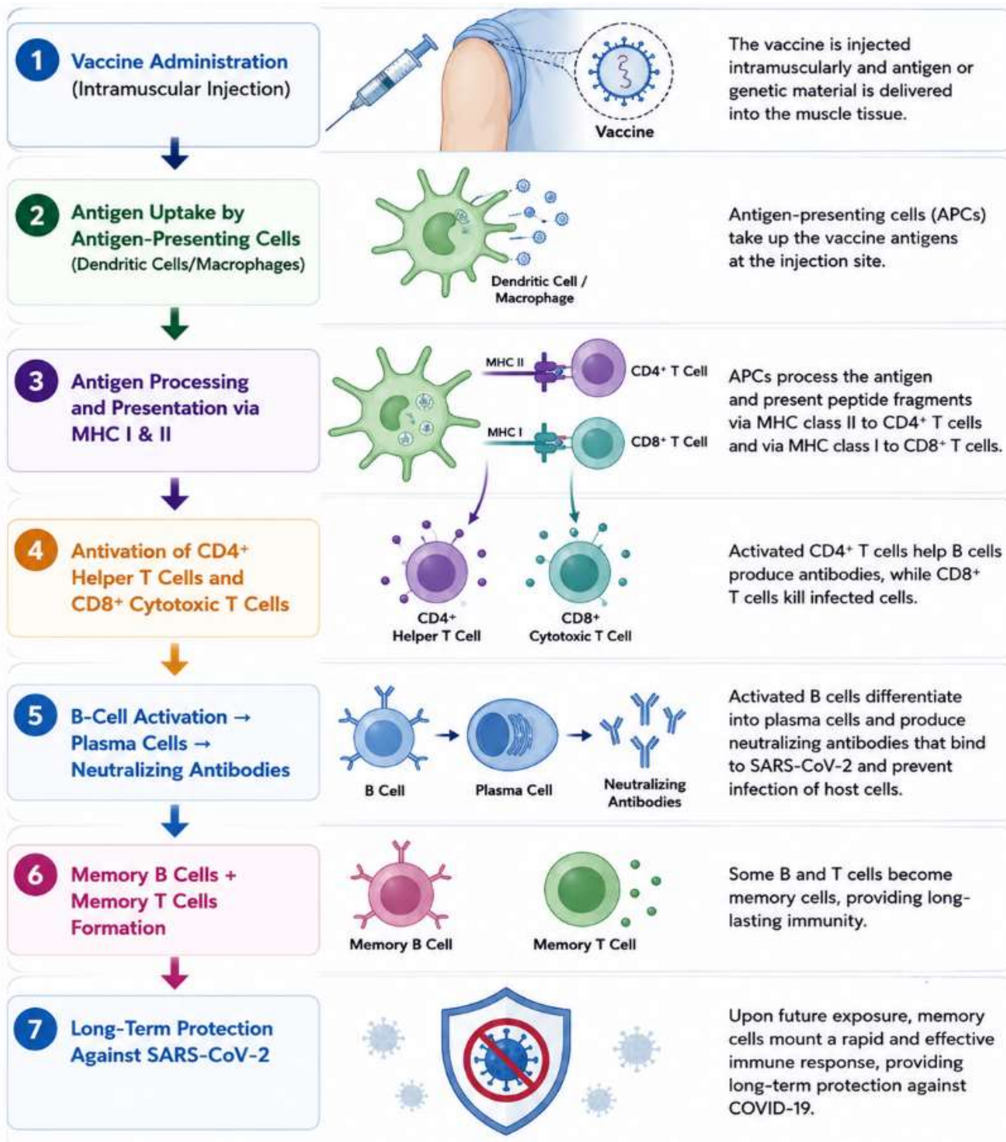


Table 2: Pharmacological comparison of major COVID-19 vaccine platforms

Vaccine Platform	Antigen Delivery	Mechanism of Action	Advantages	Limitations
mRNA	Lipid nanoparticle-encapsulated mRNA	Intracellular spike protein synthesis	Rapid development, high efficacy	Cold-chain storage
Viral Vector	Adenoviral vector	DNA delivery and spike protein expression	Strong cellular immunity	Vector immunity may reduce response
Inactivated	Whole inactivated virus	Multiple viral antigens stimulate immunity	Established technology	Often requires adjuvant and boosters
Protein Subunit	Recombinant spike protein	Direct antigen presentation	Excellent safety profile	Multiple doses may be required
DNA	Plasmid DNA	Host-cell antigen expression	Stable and easy to store	Limited global deployment

6. SAFETY EVALUATION AND PHARMACOVIGILANCE OF COVID-19 VACCINES

The rapid authorization and widespread deployment of COVID-19 vaccines highlighted the critical importance of comprehensive safety evaluation throughout the vaccine lifecycle. Although accelerated development enabled vaccines to become available within an unprecedented timeframe, safety assessment remained a fundamental component of vaccine evaluation. Extensive preclinical investigations, large-scale Phase I–III clinical trials, regulatory review, and continuous post-marketing surveillance collectively ensured that the benefits of vaccination substantially outweighed the potential risks. Consequently, pharmacovigilance became an integral element of global COVID-19 vaccination programs, providing real-world evidence to support regulatory decision-making and maintain public confidence.[3][4][5][6][7][18][19][20][27]

6.1 Safety Evaluation During Clinical Development

Safety assessment begins during preclinical studies, where vaccine candidates are evaluated in laboratory and animal models to identify potential toxicological effects, assess immunogenicity, and determine appropriate dosage ranges. Only vaccine candidates demonstrating acceptable safety profiles progress to human clinical trials.[23]

Clinical safety evaluation is performed sequentially through Phase I, Phase II, and Phase III trials. Phase I trials primarily assess local and systemic reactogenicity, tolerability, and preliminary safety in a small group of healthy volunteers. Phase II trials expand safety evaluation by including a larger and more diverse population while optimizing dose schedules and vaccination intervals. Phase III trials, involving tens of thousands of participants across multiple countries, provide robust evidence regarding vaccine efficacy and detect uncommon adverse events before regulatory authorization.[19][20]

The most frequently reported adverse reactions during clinical trials were mild to moderate and self-limiting. These included injection-site pain, erythema, swelling, fatigue, headache, fever, chills, myalgia, and arthralgia. Such reactions generally resolved within a few days and reflected normal activation of the immune system following vaccination.[18][21][27]

6.2 Post-Marketing Pharmacovigilance

Although clinical trials provide extensive safety data, they cannot identify extremely rare adverse events that occur only after millions of vaccine doses have been administered. Therefore, post-marketing pharmacovigilance is essential for monitoring vaccine safety under real-world conditions.[18]

Pharmacovigilance involves the continuous detection, assessment, understanding, and prevention of adverse events following immunization (AEFIs). Multiple international surveillance systems were strengthened during the COVID-19 pandemic to collect and analyse vaccine safety data from healthcare professionals, manufacturers, and vaccinated individuals.[18]

Major pharmacovigilance systems include:

- Vaccine Adverse Event Reporting System (VAERS) – United States
- V-safe – United States
- EudraVigilance – European Union
- Yellow Card Scheme – United Kingdom
- National AEFI surveillance programs implemented by individual countries

These surveillance systems enabled the rapid identification of rare adverse events, facilitated continuous benefit–risk assessment, and supported evidence-based updates to vaccination guidelines.[3][4][13][15]

6.3 Rare Adverse Events and Risk–Benefit Assessment

As global vaccination campaigns progressed, pharmacovigilance programs identified several rare but clinically significant adverse events associated with specific vaccine platforms. Reports of myocarditis and pericarditis, primarily among younger males following mRNA vaccination, and thrombosis with thrombocytopenia syndrome (TTS) associated with certain adenoviral vector vaccines prompted detailed investigations by regulatory agencies.[18]

Importantly, these adverse events occurred at very low frequencies, and the overall benefits of vaccination in preventing severe COVID-19, hospitalization, intensive care admission, and death consistently exceeded the associated risks. Regulatory authorities responded by updating prescribing information, revising age-specific recommendations where appropriate, and strengthening post-marketing surveillance rather than withdrawing vaccination programs.[19]

The COVID-19 experience demonstrated the importance of transparent communication regarding vaccine safety. Rapid identification, scientific evaluation, and public reporting of rare adverse events contributed to maintaining regulatory credibility and improving public trust in vaccination programs.[20][27]

6.4 Real-World Effectiveness

In addition to safety monitoring, post-marketing studies evaluated vaccine effectiveness under routine clinical conditions. Large observational studies demonstrated that COVID-19 vaccines substantially reduced the risk of severe disease, hospitalization, intensive care admission, and mortality across diverse populations. Although vaccine effectiveness against infection gradually declined because of waning immunity and the emergence of viral variants, protection against severe clinical outcomes remained consistently high, particularly following booster vaccination.[18][19]

Real-world evidence also supported the implementation of additional booster doses, heterologous vaccination strategies, and updated vaccine formulations targeting newly emerging variants. These findings emphasized that pharmacovigilance extends beyond adverse event reporting to include continuous assessment of vaccine performance throughout its lifecycle.[20][22][27]

6.5 Lessons Learned for Future Vaccine Safety Monitoring

The COVID-19 pandemic transformed pharmacovigilance into a dynamic and data-driven process supported by digital health technologies, electronic health records, and international data-sharing networks. Collaboration among regulatory agencies, healthcare institutions, academic researchers, and pharmaceutical manufacturers enabled near real-time safety monitoring on an unprecedented scale.

The experience demonstrated that effective pharmacovigilance requires transparent reporting systems, rapid signal detection, standardized causality assessment, and timely communication with healthcare professionals and the public. These innovations have established a stronger global framework for monitoring vaccine safety and will remain valuable for future pandemic preparedness and the development of next-generation vaccines.[20][22][26]

Figure 5: COVID-19 vaccine safety monitoring framework

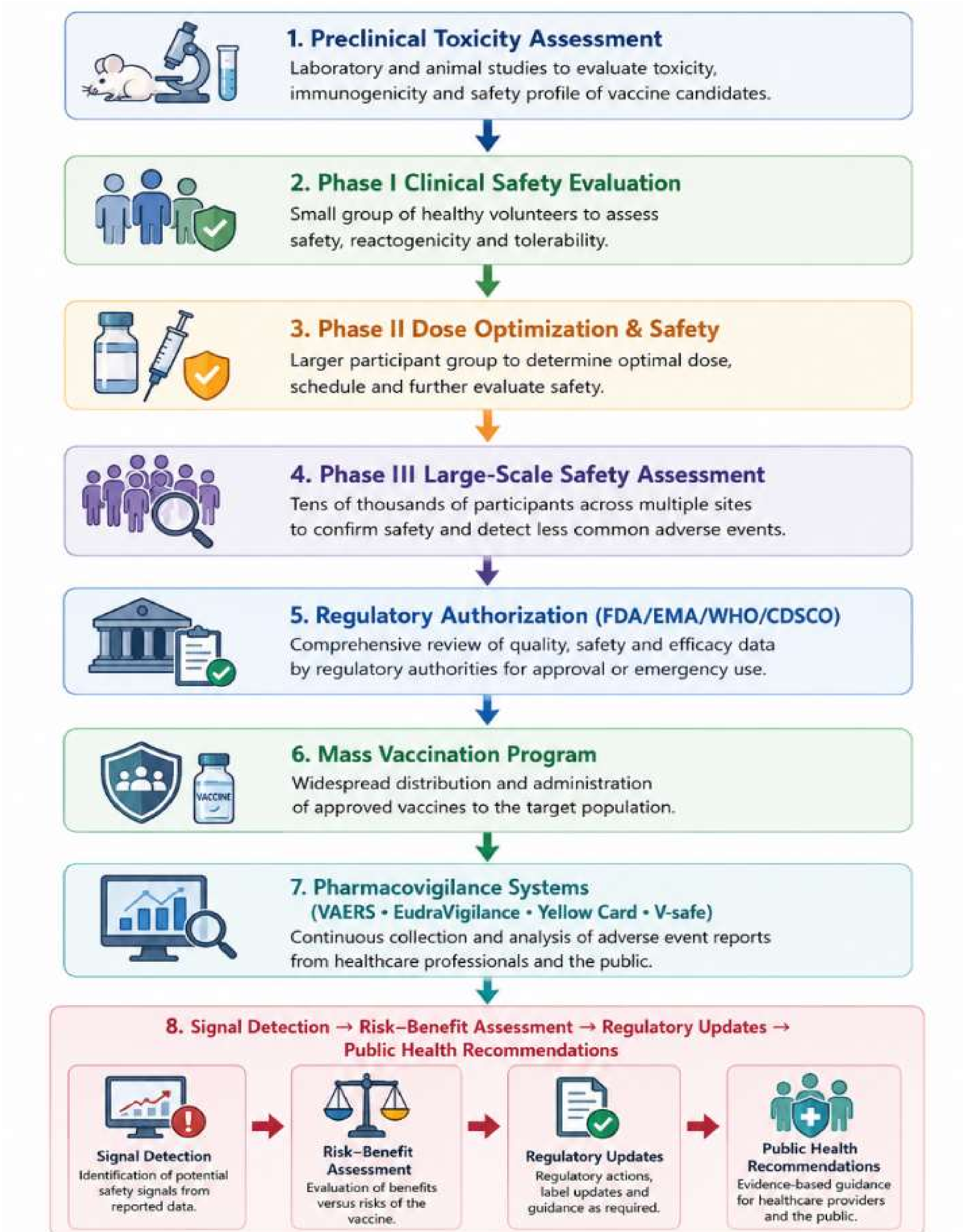


Table 3: Common and rare adverse events reported following COVID-19 vaccination

Category	Examples	Clinical Outcome
Common adverse events	Injection-site pain, fatigue, headache, fever, chills, myalgia	Mild, self-limiting, resolved within 1–3 days
Moderate adverse events	Lymphadenopathy, transient allergic reactions	Usually resolved with supportive care
Rare adverse events	Myocarditis/pericarditis, thrombosis with thrombocytopenia syndrome (TTS), anaphylaxis	Rare; monitored through pharmacovigilance systems
Long-term monitoring	Booster effectiveness, variant protection, special populations	Continuous evaluation through real-world evidence

7. FUTURE PERSPECTIVES AND LESSONS LEARNED

The COVID-19 pandemic has fundamentally transformed the landscape of vaccine research, pharmaceutical innovation, and global public health preparedness. The successful development of multiple vaccines within an unprecedented timeframe demonstrated that scientific excellence and accelerated development are not mutually exclusive when supported by strong regulatory oversight, international collaboration, and sustained financial investment. The experience gained during the pandemic has established a new framework for responding to future infectious disease outbreaks while maintaining rigorous standards of quality, safety, and efficacy.[11][18][19][20]

One of the most significant lessons learned is the value of platform vaccine technologies, particularly messenger RNA (mRNA) and viral vector systems. Unlike conventional vaccine platforms that often require years of optimization, these adaptable technologies enable rapid antigen design immediately after pathogen genome sequencing. Their successful application during the COVID-19 pandemic has expanded interest in developing vaccines against influenza, respiratory syncytial virus (RSV), human immunodeficiency virus (HIV), malaria, tuberculosis, and various emerging zoonotic diseases. Furthermore, mRNA technology is now being investigated for therapeutic applications in oncology, personalized medicine, and autoimmune disorders, illustrating its broad potential beyond infectious diseases.[19][20][27]

Advances in genomic surveillance, artificial intelligence (AI), machine learning (ML), and bioinformatics are expected to further accelerate vaccine discovery and optimization. AI-assisted antigen prediction, computational protein modelling, reverse vaccinology, and systems biology can facilitate rapid identification of immunogenic targets, improve vaccine design, and reduce dependence on time-consuming laboratory experimentation. Integration of these technologies with high-throughput manufacturing and automated quality-control systems may significantly shorten development timelines while preserving scientific rigor.

The pandemic also highlighted the importance of adaptive clinical trial designs and international regulatory collaboration. Innovative approaches such as rolling reviews, real-time data sharing, electronic clinical trial monitoring, and global multicentre studies demonstrated that administrative efficiency can be substantially improved without compromising scientific evaluation. Future regulatory frameworks should continue to encourage collaboration among international agencies, allowing harmonized review processes and more rapid access to vaccines during public health emergencies while maintaining transparency and evidence-based decision-making.[13][14][15]

Another major lesson concerns the critical role of pharmacovigilance and real-world evidence. Continuous monitoring of vaccine safety and effectiveness through electronic health records, digital surveillance systems, and global adverse event reporting networks enabled rapid identification of rare adverse events and informed evidence-based updates to vaccination policies. Strengthening pharmacovigilance infrastructure and integrating digital health technologies into routine surveillance will improve preparedness for future immunization programs and reinforce public confidence in vaccines.

Despite these scientific achievements, several challenges remain. Global disparities in vaccine access, manufacturing capacity, cold-chain infrastructure, and healthcare resources limited equitable vaccine distribution, particularly in low- and middle-income countries. In addition, misinformation, vaccine hesitancy, and unequal public health communication affected vaccine acceptance in many regions. Addressing these challenges will require coordinated international policies, technology transfer initiatives, investment in regional manufacturing capabilities, and transparent risk communication strategies to ensure equitable access to life-saving vaccines during future pandemics.[18][19][20]

Overall, the COVID-19 pandemic has demonstrated that vaccine development can be significantly accelerated through scientific preparedness, technological innovation, and coordinated global collaboration without eliminating the essential stages of preclinical evaluation, clinical testing, regulatory review, and post-marketing surveillance. The integration of modern vaccine platforms, digital technologies, adaptive regulatory pathways, and robust pharmacovigilance systems has established a sustainable model for responding to future public health emergencies. Continued investment in these areas will not only improve pandemic preparedness but also accelerate the development of safer, more effective vaccines for a broad range of infectious and non-infectious diseases.[9][8][10][18]

Table 4: Key lessons learned from COVID-19 vaccine development

Domain	Key Lesson	Future Application
Scientific research	Prior coronavirus research accelerated vaccine discovery	Expand research on high-risk pathogens
Vaccine technology	Platform technologies enabled rapid development	Develop adaptable universal vaccine platforms
Clinical trials	Adaptive and multicenter trial designs improved efficiency	Implement flexible global trial networks
Regulatory science	Rolling reviews shortened approval timelines	Harmonize international regulatory frameworks
Manufacturing	Manufacturing at financial risk increased vaccine availability	Strengthen regional manufacturing capacity
Pharmacovigilance	Real-world evidence improved continuous safety assessment	Expand digital surveillance systems
Public health	Global collaboration accelerated vaccine deployment	Improve equitable vaccine access and pandemic preparedcess

CONCLUSION

The COVID-19 pandemic marked a defining moment in the history of vaccine development, demonstrating that scientific innovation, international collaboration, and regulatory adaptability can substantially accelerate vaccine development while maintaining rigorous standards of safety, quality, and efficacy. Unlike the conventional vaccine development pathway, which generally requires 10–15 years, multiple COVID-19 vaccines progressed from genome sequencing to Emergency Use Authorization within approximately one year. This unprecedented achievement was made possible through decades of prior coronavirus research, advanced vaccine platform technologies, substantial financial investment, adaptive clinical trial designs, manufacturing at financial risk, and rolling regulatory review rather than the omission of essential scientific evaluation.

This review highlights that the fundamental principles of vaccine development—including exploratory research, preclinical studies, Phase I–III clinical trials, regulatory assessment, Good Manufacturing Practice (GMP), and post-marketing pharmacovigilance—remained integral components of the COVID-19 vaccine development process. The primary innovation was the implementation of parallel development strategies and enhanced global coordination, which minimized administrative delays and optimized resource utilization without compromising scientific integrity.

From a pharmacological perspective, the successful application of messenger RNA (mRNA), viral vector, protein subunit, inactivated, and DNA vaccine platforms has significantly advanced modern immunopharmacology. These technologies effectively stimulated both humoral and cellular immune responses, resulting in substantial reductions in COVID-19-related hospitalization, severe disease, and mortality. Continuous pharmacovigilance and real-world evidence further confirmed the favorable benefit–risk profile of approved vaccines while enabling timely identification and management of rare adverse events.

The COVID-19 experience has also reshaped regulatory science by demonstrating the value of adaptive clinical trial methodologies, international data sharing, digital pharmacovigilance systems, and harmonized regulatory collaboration. These advances provide a practical framework for responding to future public health emergencies and support the continued development of innovative vaccine technologies for both infectious and non-infectious diseases.

Despite these remarkable achievements, challenges such as vaccine hesitancy, equitable global access, manufacturing capacity, and preparedness for emerging pathogens remain significant priorities. Continued investment in genomic surveillance, artificial intelligence, platform vaccine technologies, and global research networks will further strengthen pandemic preparedness and accelerate future vaccine development.

The COVID-19 vaccine development program represents one of the most significant achievements in modern pharmaceutical science. It established a new paradigm demonstrating that accelerated vaccine development is achievable through scientific preparedness, technological innovation, coordinated international collaboration, and evidence-based regulatory flexibility while preserving the fundamental principles of vaccine safety, efficacy, and public health protection.

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