Molecular Therapy
Nucleic Acids
Review

Looking beyond the origin of SARS-CoV-2: Significant strategic aspects during the five-year journey of COVID-19 vaccine development

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It has been five years since the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and we are also approaching the five-year mark of the COVID-19 pandemic. The vaccine is a significant weapon in combating infectious diseases like SARS-CoV-2. Several vaccines were developed against SARS-CoV-2, and they demonstrated efficacy and safety during these five years. The rapid development of multiple next-generation vaccine candidates in different platforms with very little time is the success story of the vaccine development endeavor. This remarkable success of rapid vaccine development is a new paradigm for fast vaccine development that might help develop infectious diseases and fight against the pandemic. With the completion of five years since the beginning of SARS-CoV-2 origin, we are looking back on the five years and reviewing the milestones, vaccine platforms, animal models, clinical trials, successful collaborations, vaccine safety, real-world effectiveness, and challenges. Lessons learned during these five years will help us respond to public health emergencies and to fight the battle against future pandemics.

INTRODUCTION

The spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had devastating effects throughout the globe, including substantial economic loss. Massive loss of life was reported. With billions of infections and millions of deaths, COVID-19 was described as one of the most significant pandemics in history. It was a miserable period in the history.[1,2] The first case of COVID-19 was identified in Wuhan, China, at the Huanan Seafood Market, where vendors sold live mammals. During the description of the source of SARS-CoV-2, Jiang and Wang reported the wildlife trade and its trade market might be the foundation of the COVID-19 pandemic and the source of SARS-CoV-2. Therefore, this market was described as the early epicenter of this pandemic.[3,4] Different cases of pneumonia with unknown etiology were noted in Wuhan, China.[5] The causative agent was identified as the wild-type SARS-CoV-2 virus. The virus was described as a betacoronavirus family member and related to SARS-CoV.[6] The virus spread outside China. On January 30, 2020, WHO (World Health Organization) declared a Public Health Emergency of International Concern on January 30, 2020, due to the spread outside China and started spreading throughout the globe.[7] On March 11, 2020, the WHO announced the COVID-19 pandemic due to the quick spreading of the virus globally.[8] Subsequently, due to the rapid spread of infections, the pandemic hit most large countries by June 2020. The infection spread in more than 200 countries across the globe when the pandemic struck. Most countries had taken measures like isolation, quarantines, contact tracing, masking, etc. These measures aimed at slowing down and reducing the transmission. However, these countries failed to halt the pandemic.

During epidemics and pandemics, infection spreads rapidly. At the same time, it is essential to understand how lethal the infections were. Therefore, case fatality rate (CFR) is an essential parameter for understanding the intensity of a pandemic. Several researchers measured the CFR during COVID-19 from time to time. During the pandemic, a high CFR was reported more frequently in the elderly male population.[9,10] Esmaeili et al. reported high CFR in the hospitalized elderly male population.[9] Yanez et al. reported that the mortality rate was 77% higher in men than in women. At the same time, the mortality rate was 8.1 times higher among the 55- to 64-year-old age groups of people and more than 62 times higher among those aged 65 or older.[10] On the other hand, researchers were trying to understand the country-wise CFR. It was reported that Mexico had the highest CFR during COVID-19.[11,12] Italy recorded the second-highest CFR.[13] However, among European countries, Italy had the highest CFR.[14] Other significant CFRs

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were noted in France, Spain, the UK, and Russia.[14] At the same time, it was noted that CFR was positively associated with age and number or their combination.[11]

Several potential therapeutic and immunotherapeutic molecules were reported occasionally to prevent the infection of COVID-19. These molecules include remdesivir, nirmatrelvir, favipiravir, molnupiravir, and dexamethasone.[15–17] The immunotherapeutic molecules for the treatment of COVID-19 include tocilizumab and mavrilimumab.[18–20] At the same time, baricitinib, a Janus kinase inhibitor, may also be effective for moderate COVID-19 disease.[21] These therapeutic and immunotherapeutic molecules were tested through clinical trials. Numerous clinical trials were performed to evaluate therapeutic and immunotherapeutic molecules against SARS-CoV-2. However, after approval, therapeutic and immunotherapeutic molecule resistance was reported occasionally.[22] Therefore, a vaccine was one of the essential weapons used to fight against COVID-19 infection during the pandemic.

Vaccination or immunization is a key component of global health and can help transform public health by preventing disease's spread and saving lives. Vaccination can decrease healthcare costs and thus lead to economic growth by reducing the disease burden in society. It expands long, healthy lives. Vaccines are thus an efficient tool for reducing health inequities and, thus, wealth disparities.[12,23,24] Therefore, the vaccine is a powerful tool to fight against the pandemic. After the appearance of COVID-19 and the identification of SARS-CoV-2 in China, the genome of the virus was sequenced by the scientists Zhang and his colleagues at Fudan University, and the sequence was deposited to the NCBI. They had performed the metagenomic RNA sequencing of a sample. The sample was collected from a patient's bronchoalveolar lavage fluid, where scientists identified the new RNA virus strain.[25–27] After sequencing the virus, they found two closely related viruses: SARS-CoV and MERS-CoV.[26,28] They noted that the whole viral genome sequence length was about 29,903 nucleotides. They reported an 89.1% similarity between two genome sequences with SARS-CoV.[25] However, when the infection spread worldwide, and the pandemic started, everyone understood the need for vaccines to fight against the virus. Therefore, vaccine development efforts were started at the speed of the pandemic. It was found that multiple vaccine candidates were rapidly developed through the collaboration of private and public sector expertise and infrastructure. The success of this endeavor is evident in the rapid advancement of development in vaccine sectors.[29–31] It has been noted that the first COVID-19 vaccine that was documented in the clinical trial was the mRNA-1273 from the Moderna vaccine. The clinical trial was initiated in May 2020. At the same time, the second COVID-19 vaccine candidate that documented the clinical trial was BNT162b1. Pfizer commenced the clinical trial in collaboration with one German biotechnology company, BioNTech.[32,33] It was noted that the Coalition for Epidemic Preparedness Innovations worked with vaccine developers and global health authorities to support the vaccine development initiatives for COVID-19 vaccines.[33] Until today, 50 vaccine candidates have been found to be approved in at least one country. Among these vaccine candidates, WHO approved 12 vaccine candidates.[34] The previous concept of vaccine development was that it was costly and lengthy, but this changed after the COVID-19 vaccine was developed.

This review systematically discusses the lessons learned during the COVID-19 pandemic regarding vaccine development, including milestones, vaccine platforms, animal models, clinical trials, successful collaborations, vaccine safety, real-world effectiveness, and associated challenges. The lessons learned during the pandemic related to vaccine development will help fight against future pandemics.

OVERALL STRATEGIC ASPECTS: VACCINE DEVELOPMENT TO VACCINATION DURING THE PANDEMIC

Due to the pandemic, the COVID-19 vaccine was an absolute necessity. Therefore, every country had an accepted need for vaccine research and development, manufacture, and distribution. We found that a strategically ample amount of collaborative processes were performed from vaccine research to development and clinical trials. One example is the ACTIV (accelerating COVID-19 therapeutic interventions and vaccines) collaborative program for vaccine and therapeutic development, which is a public-private partnership (PPP). In this case, the strategic collaboration was developed through the PPP mode. NIH directed the collaboration. Endpoint, safety, and efficacy of the vaccine were among the issues for vaccine development. Companies have created strategies to achieve their developed vaccines' proper safety and efficacy and reach the endpoint.[35] Strategical collaboration helped to conduct the huge number of clinical trial for vaccines and therapeutics. On the other hand, after the development of vaccines, every country has developed strategies for distributing them to every corner of the country and maximum vaccination for their people.[36,37] Finally, it has been noted that the ultimate need during the pandemic was the rapid vaccine development.

OVERVIEW OF COVID-19 VACCINE DEVELOPMENT

Although there was an urgency, the vaccine development process for COVID-19 followed the same steps as other vaccines: target discovery or identification, selection of vaccine platform, design of candidate vaccines, and different human clinical trials.[38] All critical steps were completed. However, vaccine development started very early to fight the epidemic or pandemic. It might have started at the beginning of 2020. With the 2020 vaccine development completed, it was rolled out with emergency approval. Although the development of traditional vaccines takes 15 years, the COVID-19 vaccine was completed within a year.

It was understood that vaccines developed for COVID-19, like those for other diseases, completed all the necessary stages after being given emergency approval due to the pandemic. However, due to the urgency, many COVID-19 vaccines continued phase-III trials

even after they were rolled out. These stages were completed while the vaccines were already in use.

THE INITIAL STAGE OF COVID-19 VACCINE R&D: VACCINE TARGET IDENTIFICATION

Vaccine target discovery or identification is integral to identifying part of the pathogen that will be considered for vaccine design. This is one of the crucial steps of vaccine discovery.[39] For the COVID-19 vaccine target, most researchers targeted the Spike protein (S-protein) for vaccine development.[40] During the vaccine development of SARS-CoV and MERS-CoV, the S-protein was considered a vaccine target. Previous studies found that this protein is a target for T cell responses. In this direction, studies explained the antigenic $CD4^+$ and $CD8^+$ T cell epitopes of S-protein are responsible for T cell immunity in SARS-CoV and MERS-CoV.[40–42]

In the initial stage of early 2020, researchers started to identify the vaccine target for COVID-19. Several researchers were targeting the surface glycoprotein for vaccine development. Immediately after submitting the complete genome sequence in the NCBI, we mapped the T cell and B cell antigens using the S-protein of SARS-CoV-2 using computational biology.[43] At the same time, we developed an immunoinformatic-based multi-epitopic vaccine construct against SARS-CoV-2, which was docked with TLR4. The vaccine construct was published on March 5, 2020, in the *Journal of Medical Virology*.[43] It was the first vaccine construct against SARS-CoV-2, targeting the S-glycoprotein. Simultaneously, Baruah and Bose also mapped the T cell and B cell antigens using surface glycoprotein.[44]

Similarly, Ahmed et al. identified the potential vaccine targets of SARS-COV-2, where they targeted all structural proteins such as M-protein, S-protein, N-protein, and E-protein. They have identified several T cell and B cell epitopes derived from the N and S-proteins.[45] Like SARS-CoV and MERS-CoV, the antigenic $CD4^+$ and $CD8^+$ T cell epitopes of S-protein are responsible for T cell immunity against SARS-CoV-2.[40,46] Therefore, several researchers have tried identifying an effective vaccine target for SARS-CoV-2.

COVID-19 VACCINE R&D: IMPORTANCE OF S-PROTEIN DURING COVID-19 VACCINE DEVELOPMENT

S-protein is essential for vaccine development due to its high antigenicity or immunogenicity. Therefore, it is a target for vaccine development.[47] It was the main protein for vaccine development. The protein exists in the virus envelope as a homotrimer, consisting of an S1 subunit (membrane-distal subunit) and an S2 subunit (membrane-proximal subunit). It has several domains: the NTD (N-terminal domain), RBD (receptor binding domain), and C-terminal domain.[40]

Consequently, the S-protein was the main focus of every researcher's attention in vaccine development due to its three significant properties: high immunogenicity, presence of short antigenic epitopes, and presence of the antigenic domain in the RBD.[12] Martínez-Flores et al. also noted the main characteristics of the S-protein, such as the presence of short epitopes throughout the S-protein, especially antigenic domains in the RBD and the other parts of the S-protein.[48] In addition, it was reported that the S-protein is a vital target of $CD4^+$T cells. On the other hand, it was also noted that, in general, very few $CD8^+$ T cells are activated by natural infection of SARS-CoV-2.[46]

The S-protein's antigenic component induces host immune responses and neutralizes antibody production. Therefore, it helps to develop protective immunity against virus infection.[49] Byrnes et al. demonstrated that antibody targeting of the RBD domain and the proportion of anti-Spike antibodies.[50] However, several mutations in the antibody-binding regions, especially RBD and NTD, cause neutralizing antibody (nAb) escape and, thus, vaccine escape[51,52] (Figure 1).

COVID-19 VACCINE R&D: SOMETIMES, THE MODIFICATION WAS DONE IN THE S-PROTEIN RESIDUES FOR BETTER STABILITY OR HIGHER VACCINE EXPRESSION

Researchers modified the S-protein as needed for a particular platform during vaccine development. They merely modified the S-protein residues during vaccine development to improve stability or increase vaccine expression. It was noted that Janssen's vaccine was Ad26.COV2.S was related to the S-protein altered by the expression of Ad26 gene. The deletion was done in the furin site, and TAA 986–987 mutations were introduced.[53]

Similarly, the NVX-CoV2373 subunit vaccine adopts a full-length Spike containing a furin site mutation with a pre-fusion conformation. It was produced in the Sf9 insect cell expression system. This conformation of S-protein (per-fusion) is generally metastable and is usually changed into another conformation (post-fusion). By mutating two residues (V987 and K986) to proline, this mutable configuration (pre-fusion) can be stabilized.[40,54]

THE SCIENTIFIC ACHIEVEMENTS OF VACCINE DEVELOPMENT

Most of the COVID-19 vaccines were developed using next-generation vaccine platforms

Next-generation vaccines are promising, effective, and long-lasting candidates for combatting pathogens. Examples of some next-generation vaccines are nucleic acid-based vaccines such as RNA vaccines, DNA vaccines, and viral vector vaccines, which belong to this category. The majority of approved COVID-19 vaccines involve a next-generation platform. Next-generation vaccines are developed based on sequence information. These vaccines were used during COVID-19.[55–57] These vaccines help combat future pandemics again. According to WHO data (till December 05, 2024), approval for 50 vaccines were given by at least one country (Table S1), and WHO has granted 12 vaccines under emergency use listing (EUL) (Table S2). Among 50 vaccines, we explored the vaccine platform and the platform protein subunit vaccines, inactivated vaccines, viral

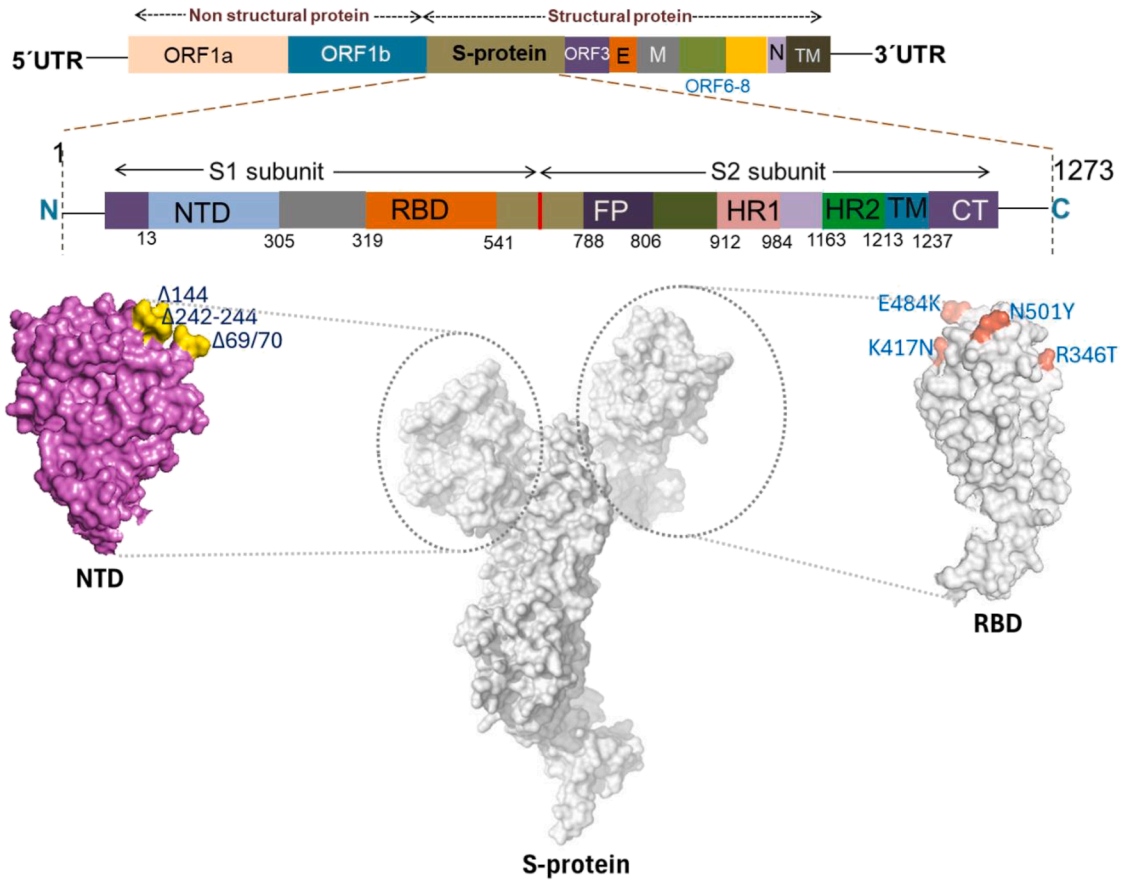

Figure 1. Spike protein of COVID-19 and its RBD and NTD mutations

vector vaccines (non-replication), DNA vaccines, and virus-like particle (VLP) vaccines (Figure 2).[58] Among these vaccines, protein subunit vaccines are the highest in percentage (30%), and inactivated virus vaccines are the second highest in percentage (28%). Others are viral vector vaccines (non-replication) (20%), mRNA vaccines (16%), DNA vaccines (2%), and VLP vaccines (2%) (Figures 3A and 3B).

Nagy et al. previously reported different platforms such as live-attenuated virus vaccines, inactivated virus vaccines, replication-deficient vectors, protein subunit vaccines, and genetic vaccines (DNA and RNA vaccines).[59] On the other hand, Kudlay et al. previously reported different platforms such as protein subunit vaccines, vaccines containing viral vector (non-replicating), DNA vaccines, vaccines containing inactivated virus, RNA vaccines, viral vector (replicating), and pathogen-specific artificial antigen-presenting cells (aAPCs).[60] From the WHO list, Krammer noted more than 180 vaccine candidates with different platforms in *Nature*, and vaccine platforms are inactivated vaccines, live attenuated vaccines, recombinant protein vaccines, replication-competent vectors, replication-incompetent vectors, inactivated virus vectors, RNA vaccines, and DNA vaccines.[32]

Inactivated vaccines are produced through viral (SARS-CoV-2) cell culture, where chemicals are used to inactivate the virus. Vero cells are used in virus culture.[61,62] Live attenuated vaccines are created by developing a genetically weakened virus to change its version. Attenuation can be acquired through different processes where unfavorable conditions have been provided to the virus, such as growth in nonhuman cells, growth at lower temperatures, or by reasonable alteration of the virus-like codon de-optimization.[32] Protein subunit vaccines can be recombinant S-protein-based vaccines that might use recombinant RBD protein or any VLP. These proteins (recombinant proteins) can be expressed through several expressions: yeast cells, mammalian cells, insect cells, etc.[63,64] DNA vaccines use plasmid DNA, produced at a large scale through the bacteria system.[65] Khalid and Poh illustrated the DNA vaccine platform of SARS-CoV-2.[66] Alamri et al. reported that, in mice, the DNA vaccine of SARS-CoV-2 produces long-lasting and robust Th1 cellular and humoral immunity.[67] RNA vaccines are a recent and next-generation vaccine. It uses the genetic information of the antigen. It has been reported that the mRNA vaccine for COVID-19 provides significant anti-SARS-CoV-2 immune responses.[68–70] However, DNA vaccines are more stable compared to mRNA vaccines. Therefore, it can be stored for a long time.[71]

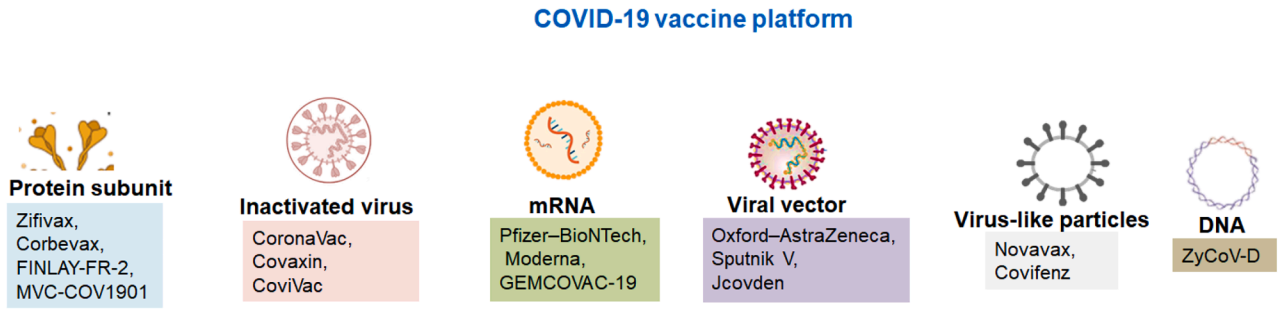

Figure 2. Figure demonstrates different COVID-19 vaccine platforms with examples

Different approved vaccines and their vaccine platform

WHO reports indicated that approval has been given 50 vaccines by at least one country. Approved protein subunit vaccines are EpiVacCorona and Corbevax. Similarly, inactivated vaccines include CoronaVac, Indian Covaxin, and Russian CoviVac. Authorized mRNA vaccines include Pfizer-BioNTech and Moderna vaccines. Approved viral vector vaccines are Oxford-AstraZeneca and Sputnik V. Authorized VLP includes Novavax. Finally, DNA vaccines include ZyCoV-D. ZyCoV-D is the only DNA vaccine approved by India and was developed by an Indian pharmaceutical company named Zydus Cadila.[72,73] The vaccine includes a plasmid DNA which contains the spike-S gene of SARS-CoV-2. Along with the S-gene, it contains a signal peptide.[73,74] mRNA vaccines are recently developed vaccines for COVID-19. Like DNA vaccines, mRNA vaccines have been carried out the genetic information for the antigen instead of the antigen itself, and the antigen is then expressed in the cells of the vaccinated person.[75,76] mRNA vaccines are two types: self-amplifying mRNA and non-replicating mRNA.[77] The approval of the COVID-19 mRNA vaccines shows promises for other infectious diseases. Therefore, other researchers have indicated that, like the COVID-19 vaccine, another mRNA vaccine can potentially control other infectious diseases.[78,79] On the other hand, viral vectors such as the modified chimpanzee adenovirus vector (ChAdOx1) or the human rAd26 can be used to express the gene of interest. Viral vector vaccines for COVID-19 used the modified chimpanzee adenovirus vector (ChAdOx1) that carries the gene of interest (Spike protein).[29] It has been noted that most of them induce effective immunity. All the vaccines are produced by a standardized manufacturing process, facilitating a rapid clinical evaluation.

Previously, one COVID-19 protein subunit vaccine (NVX-CoV2373) was approved by the WHO and authorized only for emergency use. It has also been noted that it is independently developed in China. The WHO approved the CoronaVac and BBIBP-CorV.[30]

First authorized vaccine against SARS-CoV-2 and WHO-approved vaccines

The first two vaccines were authorized, i.e., the BNT162b2 vaccine from Pfizer, which is known as Pfizer-BioNTech. Another vaccine was mRNA-1273 from Moderna, which is known as the Moderna mRNA vaccine (Figure 4).[12,80,81] Both of these vaccines are mRNA vaccines. These two vaccines were granted emergency use authorization (EUA) for use in two countries, i.e., USA and Europe. The EMA and USFDA granted EUA for these two vaccines for use in Europe and the USA at the end of 2020 or early 2021.[12,80] However, the

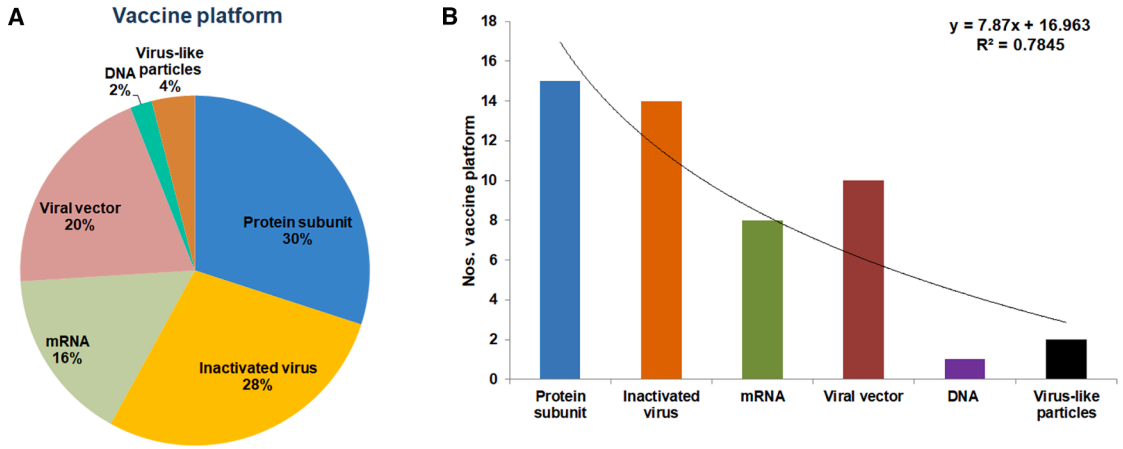

Figure 3. The figure depicts percentage and number of different COVID-19 vaccine platform

(A) Pie chart shows the percentage of different COVID-19 vaccine platforms, (B) bar diagram shows the number of different COVID-19 vaccine platforms.

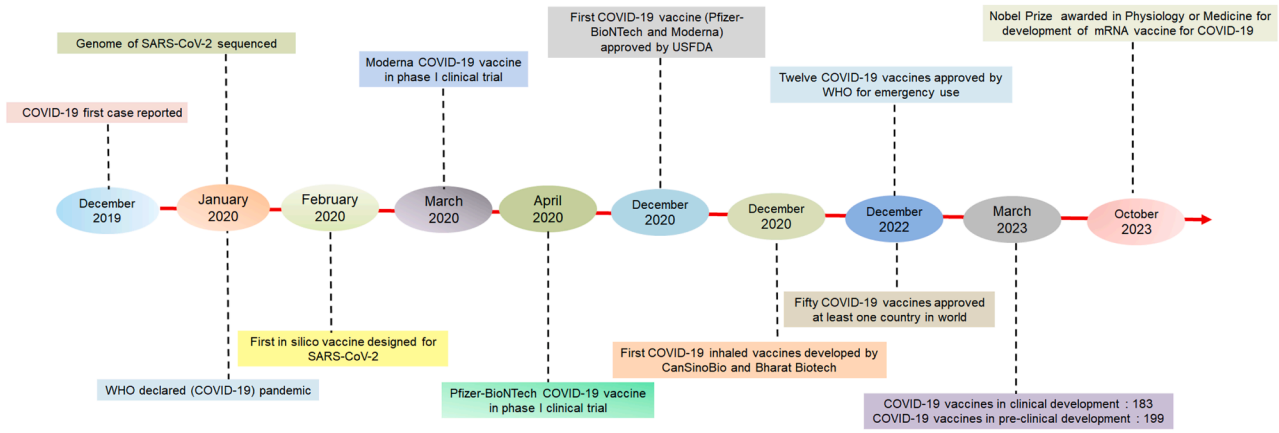

Figure 4. The figure demonstrates the different significant milestones of the COVID-19 pandemic and vaccines development

WHO granted EUL to 12 vaccines which are Nuvaxovid (Novavax), COVOVAX (Novavax formulation) (Serum Institute of India), Comirnaty (Pfizer/BioNTech), SKYCovione (SK Bioscience Co Ltd), Spikevax (Moderna), Vaxzevria (Oxford/AstraZeneca), Convidecia (CanSino), Jcovden (Janssen [Johnson & Johnson]), Covishield (Oxford/AstraZeneca formulation) (Serum Institute of India), Covaxin (Bharat Biotech), Covilo (Sinopharm, Beijing), and CoronaVac (Sinovac) (Table S1). At the same time, it has been noted that 12 vaccines were approved by at least one country (Table S2).

COVID-19 vaccine-mediated immunity

After vaccination, the immune response is elicited by the vaccine in the body. Vaccine-induced immunity is called acquired immunity or active immunity. During the antigen processing, APC is complexed with the $CD4^+$ T with the help of major histocompatibility complex class II (MHC class II). It helps in the differentiation of helper T cells (Th cells). Th cells produced cytokines like IL-2, IFN-γ, IL-4, etc. Similarly, APC is complexed with the $CD8^+$ T with the help of MHC class I. It helps differentiate cytotoxic T lymphocytes (CTL) (Figure 5). CTL can kill the infected cells and produce perforin and granzyme.

On the other hand, activated Th (T helper) cells relocate to the lymphatic follicles and afterward differentiate into T follicular helper cells or Tfh cells. These cells belong to a type of $CD4^+$ T cells. It induced B cells. B cell produces two types of cells: memory B cell and plasma cell. Again, plasma cells produce nAb (Figure 5).

However, vaccines can produce or induce nAb to protect the vaccinated individuals. On the other hand, viral vector and mRNA vaccines of COVID-19 are reported to activate Th1 cells to induce their responses.[82,83]

Several researchers have reported that the COVID-19 vaccine activates and induces Th1 cell responses. Type 1 T helper cells (Th1 cells) are a subset of T helper cells.[84] These groups of cells activate other immune cells, which produce cytokines. Several researchers reported that these vaccines, BNT162 (mRNA vaccine BNT162b1 and BNT162b2), mRNA-1273 (mRNA vaccine includes BNT162b2 and BNT162b1), NVX-CoV2373 (protein subunit vaccine), and ChAdOx1 nCoV-19 (viral vector vaccine), induce Th1 cells.[69,82,85,86] On the other hand, different COVID-19 vaccines, such as NVX-CoV2373, help to differentiate activated $CD8^+$ T cells into CTLs to boost immunity (cellular immunity) further. Additionally, Th1 cells can secrete TNF-α and IFN-γ.[87] On the other hand, several researchers reported that mRNA vaccines can trigger efficiently virus (SARS-CoV-2) antigen-specific responses of germinal center B cell (GC B cell).[88–90] GC B cell is the main resource of memory B cells and plasma cells that produce antibodies in the human body.[91]

Animal models during vaccine development

Different animals have been used in developing COVID-19 vaccines and testing their antigenic responses to vaccines. These animal models are nonhuman primates, ferrets, golden hamsters, and mice.[92,93] Nonhuman primate models include African green monkeys (*Chlorocebus aethiops*), rhesus macaques (*Macaca mulatta*), and cynomolgus macaques (*Macaca fascicularis*).[93] These nonhuman primate models are occasionally used in vaccine development. Other animal models, such as mink, cats, dogs, pigs, chickens, ducks, etc., have been used.[92,93]

The WHO approved the different animal studies of COVID-19 vaccines. After approval, different COVID-19 animal models have been used for vaccine development. Besides vaccine development, these models are used for several experiments related to SARS-CoV-2 infection, pathological manifestations, transmissibility, etc. Here, the animal model includes hamster, ferret,[94,95] mouse-adapted SARS-CoV-2 virus (a virus variant adapted for use in mice),[96,97] mice expressing human ACE2,[98–100] golden Syrian hamster model,[101] and nonhuman primate models.[102–104] However, the immunogenicity of vaccines was tested in animal models from time to time. Wang et al. have tested the BBIBP-CorV vaccine's immunogenicity in guinea pigs, rabbits, and BALB/c mice.[61] Similarly, CoronaVac is an inactivated vaccine known as PiCoVacc. The vaccine was reported as highly

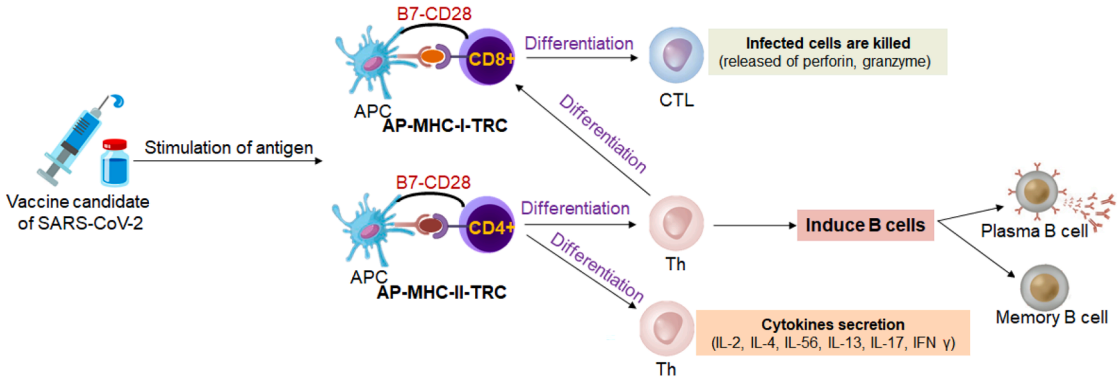

Figure 5. Vaccine-induced T cell and B cell response

immunogenic in BALB/c mice.[61] Van Doremalen et al. found that the ChAdOx1 nCoV-19 vaccine (adenovirus-vector-based vaccine) induced a balanced cellular and humoral immune response of Th cell (type 1 and type 2) in rhesus macaques and was able to prevent SARS-CoV-2 induced pneumonia.[105] Mercado et al. reported that the Ad26 vaccine (single-shot) can provide protective immunity against SARS-CoV-2 in rhesus macaques. In this study, researchers evaluated the vaccine-elicited nAb titers and correlated them with protective efficiency. The result suggested a correlation between immune protection.[53] mRNA vaccine was tested in animal models and provided sufficient protective immunity. Corbett et al. evaluated the immune protection of the mRNA-1273 vaccine in nonhuman primates. The mRNA-1273 vaccine induced Th1-related CD4 T cell responses.[106] Similarly, the mRNA vaccine BNT162b vaccine was tested in an animal model and found to have protective immunity. After testing in the rhesus macaques, Vogel et al. reported that BNT162b vaccines provide immunity by triggering the Th1 and IFNγ. They evaluated dose-dependent antibody response with virus-entry inhibition through the titers. They noticed robust IFNγ+CD8+ T cell and Th1 CD4+ responses, and the vaccine candidate protects the SARS-CoV-2 challenge macaques.[107] Therefore, a variety of animal models helps us with vaccine development by evaluating the protective immunity elucidated by the vaccine.

Preclinical findings are essential for vaccine development, and they provide information to inform dose optimization or safety profiles. This information is vital to entering into the clinical trial. One such preclinical model is MRT5500 in preclinical animal models. This model elicited potent nAbs as measured in neutralization assays in Syrian golden hamsters and non-human primates (NHP). In this work, immunization was performed using five μg per dose with the six S-protein associated mRNA vaccines. After the serum dilution, the study noted that neutralizing potency was achieved with 50% inhibition of reporter pseudoviral particles (RVP) entry (ID50). This MRT5500 induced robust dose-dependent binding and nAb responses. It shows the dose-dependent nAb responses after the first immunization, and the second one enhanced it. Here, four vaccine formulation doses were tested, which were 0.15, 1.5, 4.5, or 13.5 μg. Except for the one-dose regimen, differences between titer groups (1.5, 4.5, and 13.5 μg) were not statistically significant. However, compared to the sham-vaccinated control, two doses of 0.15 μg and a single dose of 1.5 μg or higher demonstrated particular levels of protection. At the same time, Th1-biased T cell responses evaluated IFNɣ and IL-5 (ELISPOT D35 data for 5 μg and 10 μg doses), and IFNɣ in 5 μg showed better results. This robust model produced TH1-biased responses in both NHP and mouse.[108] Recently, Li et al. reported that SARS-CoV-2 S-protein produced in insect cells can produce neutralization titers in NHP. The vaccine contains an aluminum adjuvant. Researchers reported that higher doses, such as 20 μg of vaccine dosage, can elicit high neutralization titers in NHP. Higher doses (20 μg) of S-2P in NHP can produce increased neutralization titers.[109] DiPiazza et al. developed an mRNA-1273 vaccine applied in mice to understand the vaccine dose. In this study, the researchers applied the vaccine with doses of 0.1, 0.2, and 1 mg. They found that immunization with 1 mg showed IC50 in mice. They found that 0.1 mg of vaccine dose elicited lower binding antibodies than both the doses (0.2 and 1 mg). The overall study result shows reduced viral replication without disease enhancement.[110] However, several studies were performed for dose optimization or safety profiles using animal models.

VACCINES CLINICAL TRIALS

All developed COVID-19 vaccines should undergo clinical trials to understand their dosages, effectiveness, and safety in humans. During COVID-19 vaccine development, phase I/II trials focused on dose fixation, safety, and effectiveness.[38,111,112] Here, researchers tried to evaluate the vaccine's immunogenicity. They analyzed the nAb produced against the S-protein of SARS-CoV-2 after vaccination and the duration of the nAb production to calculate the booster doses of vaccination.[113–115]

Phase III clinical trials should be double-blind, randomized, and placebo-controlled. Following these parameters, a minimum of two months of safety and effectiveness data was needed for consideration for the COVID-19 vaccine's EUA approval.[38] The FDA was furnished with the input during the clinical trial design. It was noted that the phase I clinical trial of the COVID-19 vaccine started in March 2020.[32]

WHO informed that 821 vaccine clinical trials initiated 242 developed vaccine candidates. These clinical trials were conducted in 80 countries. It was reported that 92 vaccines were conducting phase III clinical trials.[116] Nasrallah et al. reported that 1,308 clinical trials were registered. Most clinical trials were registered with the USA's Clinical Trial Registry (ClinicalTrials.gov) and the Chinese Clinical Trial database (Chinese Clinical Trial Registry). They found 703 clinical trials from the USA Clinical Trial Registry (53.7%) and 291 clinical trials from the Chinese Clinical Trial Registry (22.2%).[117]

On the other hand, Gianola et al. reported clinical trials were reported that most of the clinical studies were registered at three clinical trial platforms, which are Clinicaltrials.gov, EU Clinical Trials, and the Chinese Clinical Trial Registry. They found that these Clinical Trial Registries registered 57.9%, 98.9%, and 49.5% of clinical trials, respectively.[118] Nevertheless, these two reports included vaccine- and therapeutic-related clinical trials. However, it was clear that a relatively massive number of clinical trials were registered for COVID-19 vaccines. The world has never seen massive clinical trials for a single or infectious disease.

PANDEMIC SPEED: A NEW PARADIGM FOR VERY FAST VACCINE DEVELOPMENT

COVID-19 vaccines were developed very rapidly to fulfill the pandemic needs. Lurie et al. illustrated the rapid vaccine development procedure as pandemic speed.[119] However, different researchers described the quick development of vaccines using different terms from time to time, such as "pandemic speed," "lightning-fast quest," or "fast vaccine development."

The entire process, from vaccine conceptualization to development and finishing the clinical trial for EUA approval, was completed very quickly to fight against COVID-19. Lurie and his colleagues stated that although it was a novel platform (mRNA vaccine), the COVID-19 vaccine developed quickly, along with several challenges, such as high mortality. They described it as pandemic speed.[119] The vaccine received EUA approval within a year and was started rolling.[12] Ball describes the speedy process of COVID-19 vaccine development, which was described as the "lightning-fast quest." However, this will change the future of vaccine research and development (R&D) science.[120] It advances vaccine development research, platforms, clinical trial landscapes, and regulatory processes.

Similarly, Graham described the fast development of the COVID-19 vaccine to prevent the pandemic. This fastest-developed vaccine can generate antibody-mediated immunity.[121] Before the vaccine was approved, everybody waited to see when it would be approved, as the world was passing through a critical pandemic. However, COVID-19 vaccine approval and availability enormously benefitted the society during the critical pandemic with different VOIs and VOCs. However, it was the fastest vaccine development process the world has ever seen previously. It has changed the vaccine concept about its developmental timescale and expenses.

SAFETY ISSUES OF THE COVID-19 VACCINES

Vaccine-mediated complications were reported from time to time. Researchers reported several complications, such as thrombocytopenia, myocarditis, vaccine allergy, functional neurological disorder (FND), Bell's palsy, lymphatic diseases, etc.

During COVID-19 vaccination, myocarditis and thrombocytopenia were the most prominent safety-related issues. These were significant challenges among vaccine-mediated complications. Within seven days of receiving the second dose of an mRNA COVID-19 vaccine, myocarditis and pericarditis complications were noted as adverse events in adult-young males with an age group of 12–30 years. Cases have also been reported in females after another doses. It was also found in other age groups. Myocarditis and pericarditis cases occurred as infrequent adverse events following vaccination with mRNA vaccine.[122,123] One study indicates vaccine-associated myocarditis, which was reported at about 0.95 per 100,000 individuals. It was noted in men in the 18–24 years age group. All the individuals in these groups received two doses of the vaccine. Among female recipients, it has been noted that vaccine-associated myocarditis was about 0.69 cases/100 000.[122] Heidecker et al. reported that the highest risk group developing myocarditis is male individuals with the age group of 12–30 years within 1–14 days post-vaccination after the second dose.[123]

Immune thrombocytopenia is another adverse event noted after using vaccines such as Pfizer, Moderna, and Covishield. However, it was noted as a rare side effect.[124,125] A case report by Sivaramakrishnan and Mishra reported a patient with vaccination-associated immune thrombocytopenia due to Covishield vaccination (ChAdOx1 nCoV-19). The patient was noted with a platelet count of about 8×10^9/L. Generally, the patient's platelet count at presentation was 160×10^9/L. A week later, the platelet count was noted as 258×10^9/L.[124] Similarly, Lee et al. illustrated vaccination-associated thrombocytopenia in all 20 cases in which patients received Pfizer and Moderna vaccines. Here, the platelet count of average cases was noted below 10×10^9/L (range $1–36 \times 10^9$/L).[125] This complication after the COVID-19 vaccination was noted in the vaccinated individuals as vaccine-induced thrombocytopenia, a category of coagulation dysfunction.[126] Greinacher et al. reported cases of unusual thrombotic events after the vaccination with ChAdOx1 nCov-19. They found two patients with confirmed cases of PF4-dependent platelet activation.[127] Another complication after the COVID-19 vaccination was reported as myocarditis. It is a heart-related complication.[128] Larson et al. reported myocarditis after mRNA-1273 and BNT162b2 vaccination.[129] An allergic reaction, often called vaccine allergy, was noted occasionally after vaccination.[130] Moghimi also reported an allergic reaction after the LNP-based COVID-19 vaccines.[131] Another nervous-related disorder was reported due to the adverse effects of the COVID-19 vaccination. It includes FND. Kim et al. demonstrated how FND is activated due to COVID-19 vaccination.[132] Several other researchers reported facial paralysis. Ozonoff et al. reported Bell's palsy, the facial paralysis

due to facial nerve damage due to the COVID-19 vaccination.[133] Wan et al. reported Bell's palsy due to the vaccination with two COVID-19 vaccines such as BNT162b2 (mRNA vaccine) and CoronaVac (inactivated).[134] COVID-19 vaccine may lead to lymphatic diseases, such as abnormal lymph nodes. Nawwar et al. reported the lymphatic diseases Oxford-AstraZeneca COVID-19 vaccination.[135] Eifer and Eshet reported that an elderly female (72 years) was diagnosed with relatively increased uptake in two right axillary lymph nodes after the Pfizer-BioNTech COVID-19 vaccination. It was diagnosed with an FDG-PET/CT scan.[136] Adverse effects of this vaccination might be linked with different diseases, such as allergies, myocarditis, and thrombosis, and the number of adverse events is less compared to the vaccinated population.

The safety concerns influenced public perception, regulatory decisions, and future vaccine strategies. Concerns about vaccine safety have significantly influenced public perception of the COVID-19 vaccination program, leading to vaccine hesitancy in different populations in many countries. Despite vast scientific evidence to support the safety and efficacy of the COVID-19 vaccine, individuals were worried about possible side effects that disturb the COVID-19 vaccination program process. Occasionally, it was amplified by social media.[137,138]

Evidence of safety was an essential part of each regulatory submission for a COVID-19 vaccine and a key factor in the regulatory decision-making process. Every COVID-19 vaccine developer gathered more safety evidence during vaccine clinical trials as safety evidence.[139–142] The safety concerns about the COVID-19 vaccine influenced future strategies, such as prioritizing safety in design and transparent data sharing. During vaccine development, more focus should be given to choosing vaccine platforms that consider the safety profiles.[140] There are age restrictions on COVID-19 adenovirus-based vaccines.[143] Clinical trials of several adenovirus-based vaccines were conducted for people aged 18 years or older to understand immunogenicity and safety.[85] On the other hand, the vaccine is generally recommended for everyone aged 6 months by the US-CDC. No FDA-approved or FDA-authorized COVID-19 vaccine exists for children younger than 6 months.[144] The USCDC recommends this vaccine booster dose for all individuals above 18 years.[145] It has been found that there is an adjustment in booster dose recommendations. The Australian Technical Advisory Group on Immunization advises an additional booster dose of this vaccine to augment vaccine protection before winter for special population groups.[146] The American Academy of Family Physicians recommended individuals aged 65 years or older, who were given a COVID-19 vaccine in 2023–2024, should obtain an additional dose.[147]

Lipid nanoparticles (LNP) are now used in therapeutic delivery and are essential for vaccine delivery, such as the mRNA vaccine.[148] However, nanoparticles have been noted to provide an inflammatory response.[149] In this direction, for safety, researchers are improving LNP for use in vaccine delivery.

However, LNP were modified in mRNA vaccines to mitigate inflammation. Several researchers tried to develop modified LNPs for mRNA vaccines to mitigate inflammation. Dexamethasone (Dex) is an anti-inflammatory corticosteroid. Sometimes, Dex had been incorporated to LNPs to mitigate inflammation.

Zhang et al. developed the Dex-incorporated LNPs, which reduce LNPs' inflammatory responses. The formulation might improve the protein expression of various mRNA therapeutics.[150] Recently, the encapsulation of Dex into mRNA-LNP is another promising approach for targeted therapeutic delivery. Rivero Berti et al. recently confirmed DX integration into the LNP core, which helps Dex release slowly *in vitro* conditions over 48 h. It has been noted that high mRNA encapsulation efficiency was high with this Dex-associated LNP, which is about 95%–100%. It was effectively transfected to hPBMCs, dendritic cells, and HepG2 cells.[151] However, researchers are trying to shape next-generation vaccine development through safety concerns through shaping the next-generation vaccine development through the modifications of LNP.

REAL-WORLD VACCINE EFFECTIVENESS

The vaccine effectiveness of the COVID-19 vaccines was measured occasionally. The first efficacy data of the Pfizer and Moderna mRNA vaccine were published in November 2020, a fantastic announcement by these two companies. Pfizer and Moderna announced that these two vaccines had 94%–95% efficacy against the COVID-19 infection.[152] SARS-CoV-2 has gained huge mutations, especially Spike protein regions. After gaining mutation, different variants of SARS-CoV-2 have been developed. Due to the development of different variants, vaccines were tested for their efficacy against the different variants.

These variants have the vaccine escape property. The vaccine effectiveness of the COVID-19 vaccines was measured occasionally against these variants (Table 1). Omicron was the most escapist variant of the vaccine. A combination of vaccines was used as a heterologous booster (BBIBP-CorV/ZF2001). Notably, 80% of the vaccine candidates were unsuccessful to neutralize the Omicron variant (B.1.1.529).[153] One study conducted at Israel indicated that the fourth dose of the mRNA-1273 or BNT162b2 vaccine cannot prevent Omicron infection.[30] However, developing the different variants and subvariants of vaccine escape was common during the pandemic.[52,136,154] Therefore, researchers urge a pan SARS-CoV-2 vaccine to be more effective against the variants and subvariants.[155]

SEVERAL VACCINES HAVE DEVELOPED AGAINST THE SUBVARIANTS OF OMICRON

During the Omicron era, several subvariants of Omicron have been developed, which have been described as a "variant soup" or "a swarm of variants."[167,168] Due to RBD and NTD mutations, the subvariants can escape most of the vaccine-induced nAbs and, consequently, the vaccines. Due to the subvariants of Omicron mini surges, they were noted in different countries. However, several companies have developed vaccines for the subvariants of Omicron.

Table 1. Efficacy of different COVID-19 vaccines against significant variants of SARS-CoV-2

Sl. No.	Vaccine name	SARS-CoV-2 variants					Reference
		Alpha	Beta	Gamma	Delta	Omicron	
1	AZD1222	70.4%	83%	48%	67%	62.4%	Emary et al.; Struyf et al.; Lopez Bernal et al.[156–158]
2	BBIBP-CorV	Unknown	32.16%	Unknown		40.8%	Castelli et al.[159]
3	NVX-CoV2373	85.6%	60%	Unknown	Under investigation		Mahase; Sadoff et al.[160,161]
4	Ad26.COV-2-S	70.2%2	51.9%2	36.5%262	Unknown	72%	Sadoff et al.; Solforosi et al.[161,162]
5	BNT162b2	89.5%	75%	88%	87%	45.7%	Abu-Raddad et al.; Nasreen et al.; Andrews et al.[163–165]
6	CoronaVac	Unknown		50%	Good result	Unknown	Simoes and Rodriguez-Lazaro[166]

One example is Pfizer/BioNTech's Comirnaty Bivalent Original/Omicron BA.1 vaccine. Another is the Comirnaty Bivalent Original/Omicron BA.4/BA.5 vaccine developed by the same company. Both these vaccines are mRNA vaccines. Comirnaty Bivalent Original/Omicron BA.1 vaccine is approved by 35 countries, and Comirnaty Bivalent Original/Omicron BA.4/BA.5 vaccine is approved by 33 countries.[58,169–171]

DIFFERENT VACCINE ADMINISTRATION ROUTES

Most COVID-19 vaccines, such as mRNA vaccines, are administered through the injectable route. An intramuscular (IM) injection has been given to the vaccinated person. Other than the injectable route, the COVID-19 vaccine has been tried to be given through other routes, such as oral, electroporation (EP), and inhalation (Figure 6).

The EP technique delivers macromolecules such as nucleic acids into cells. This method is used to deliver DNA vaccines.[172] The INO 4800 is a DNA vaccine developed by INOVIO pharmaceutical, and the (EP) delivery system was used to deliver the INO 4800 vaccine. The EP delivery system is called CELLECTRA. The vaccine is developed using the full-length spike antigen.[173,174]

Researchers have tried to deliver the COVID-19 vaccine through the oral route using tablets such as VXA CoV2-1. This is the first oral tablet COVID-19 vaccine in the USA.[175]

Another vital method of next-generation vaccine delivery is the respiratory route. The COVID-19 vaccine was tried to be delivered through the inhalation route. These two inhaled COVID-19 vaccines were approved for respiratory mucosal delivery. It has been noted that the respiratory route also furnishes robust defense against different variants of SARS-CoV-2.[176] These designed vaccines are used for IM immunization.[177]

Recently, China and India have developed two COVID-19 vaccines, and Biologics Inc., China, and Bharat Biotech, India, developed these two vaccines. These two countries approve these two vaccines.[178] Examples of two intranasal SARS-CoV-2 vaccines are NasoVAX and iNCOVACC (BBV154).[179,180]

SUCCESSFUL COLLABORATION DURING VACCINE DEVELOPMENT

Collaboration is one of the main initiatives during the COVID-19 pandemic to fight the race against the pandemic.[31,181,182] A considerable number of collaborations were made during the vaccine development. It has been noted that about one-third of vaccines were developed through partnerships. Here, different collaborations were involved, such as private entities, public-public entities, or hybrid entities, called PPP. Druedahl et al. reported that these partnerships were made especially for knowledge-sharing and materials-transfer partnerships.[181] Zhou has demonstrated international collaborations for intense global (R&D) actions.[183] The US government established a PPP to speed up the development, production, and distribution of COVID-19 vaccines. Public-private partnerships were also established for therapeutics and diagnostics for COVID-19. However, most of the collaborations during the pandemic for vaccine development were highly successful.[38]

Strategic collaborations were made between organizations that share expertise and resources strategically to achieve a common goal. Strategic collaborations immensely impacted positively during the pandemic. It strengthened the health systems, developed the vaccine rapidly, achieved the goal of vaccination, and helped to prepare for the next pandemic. Strategic collaborations were developed in international, cross-sector collaboration and partnerships across multilateral organizations, governments, and the private sector. They provided broader operations at different levels during the pandemic.[181,184] One example of strategic collaboration was knowledge and data sharing during the pandemic.[184,185]

Another strategic collaboration was the ACTIV established on April 17, 2020 in the USA. The ACTIV developed through the PPP (PPI) mode. NIH led this strategic collaboration and the endeavor to unite all sectors for therapeutic interventions and vaccines for the vaccine during COVID-19.[186] In this strategic collaboration, clinical trials were one of the primary focuses. The master protocol design for clinical trials was mentioned in the ACTIV TX-Clin WG's first published article by LaVange et al.[187] Some trial-related master protocols are ACTIV-1, ACTIV-3, ACTIV-3B, ACTIV-4A, ACTIV-HT,

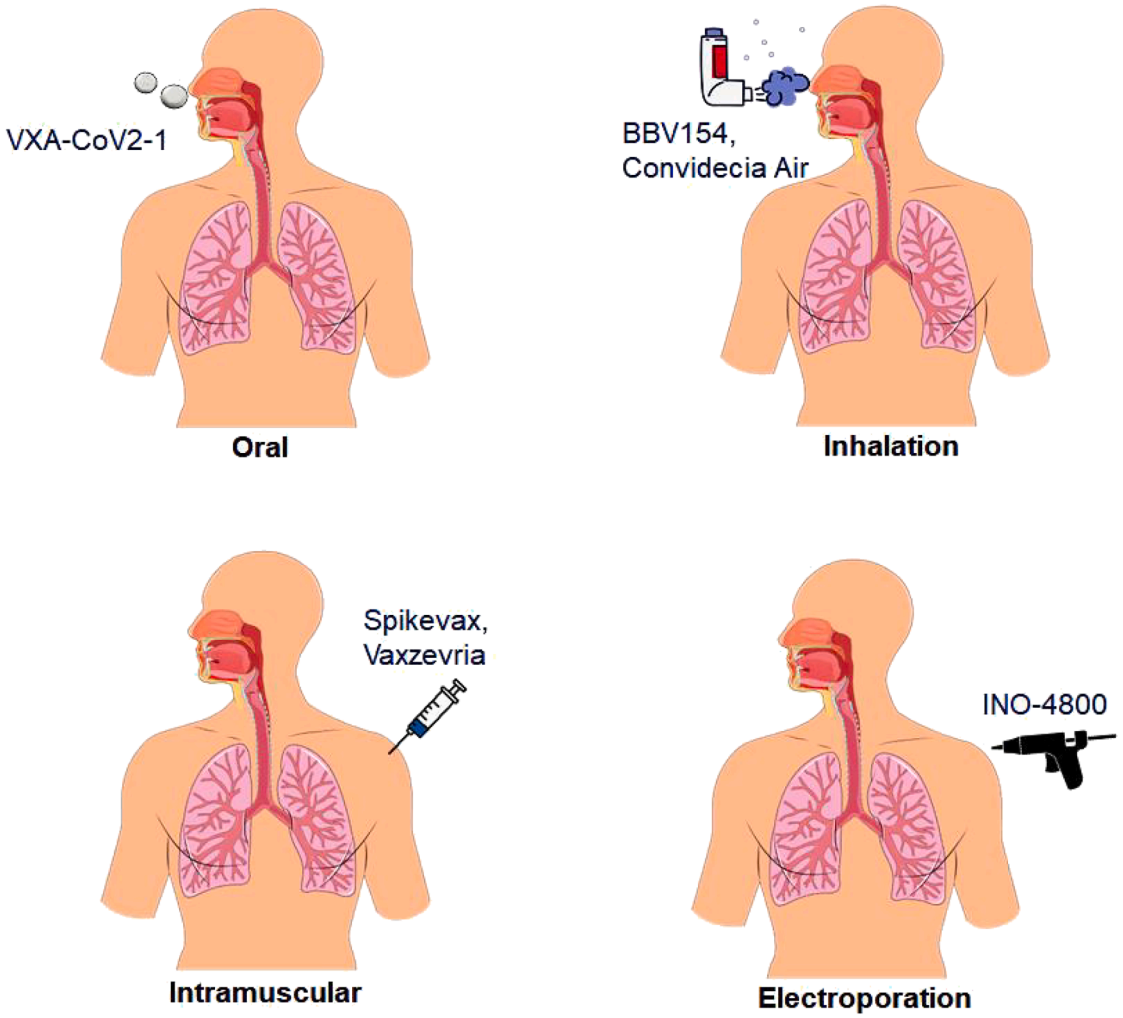

Figure 6. Different routes of administration of the COVID-19 vaccines with some examples

ACTIV-5, ACTIV-2/2D, ACTIV-4B, ACTIV-6, and ACTIV-4C. In terms of therapeutics, some successful outcomes are infliximab and abatacept, which show positive benefits. Unsuccessful outcomes are risankizumab, lenzilumab, danicopan, ivermectin (400), ivermectin (600), etc. On the other hand, the other outcome of the strategic collaboration was excellent. More than 26000 participants were enrolled in ACTIV trials. More than 600 sites were enrolled as participants in ACTIV trials. More than 54 scientific publications on ACTIV trials were published in 17 journals. This publication received immense citations, which were cited more than 2034 times.[188,189] The ACTIV working group has further provided some crucial recommendations, which are very important for evaluating potential COVID-19 therapeutics candidate selection, based on some criteria. The recommendations include: first, it is necessary to develop clear criteria for candidate selection, and we should facilitate assessing the possible development of COVID-19 therapeutics. Second, a steering committee should be formed to rank the potential therapeutic candidates, and they should rank the therapeutic candidates by considering different factors like the mechanism of action, safety data profile, and preclinical data. Utilizing efficient trial designs, openly sharing protocols, and prioritizing diverse patient populations to expedite research and identify effective treatments quickly. Third, various potential therapeutics with different mechanisms of action must be created to avoid redundancy. Fourth, it is necessary to set clear benchmarks to prioritize candidates for evaluation in clinical trials. Fifth, it is necessary to design the trial efficiently, and protocols should be shared openly.[190,191] Other than these, we found the free exchange of information and knowledge in this strategic collaborative platform during the COVID-19 pandemic, and all responses might benefit all stakeholders. Therefore, this strategic collaborative model is one of the significant models during this PHE (public health emergency). It can be considered as best practice for future pandemics. Besides the PHE or pandemic, this strategic collaborative model is significant in the routine healthcare system and might revolutionize science.

NOBEL PRIZE FOR COVD-19 mRNA VACCINE DEVELOPMENT

In 2023, Katalin Karikó and Drew Weissman were awarded the Nobel Prize in Physiology or Medicine for developing mRNA-based COVID-19 vaccines. Karikó developed LNP (lipid nanoparticle)-encapsulated nucleoside-improved mRNA vaccines against COVID-19.[192,193] Karikó developed an mRNA vaccine, BNT162b2, formulated using LNP, demonstrating 95% efficacy against COVID-19. The mRNA vaccine encoding the S-protein of SARS-CoV-2 stabilized in its per-fusion conformation.[83] At the same time, Drew Weissman was also provided the Nobel Prize for his contribution to the quick formulation of efficient LNP-based mRNA vaccines against SARS-CoV-2.[89,194,195] However, this is a great recognition to the COVID-19 vaccine researcher for their contribution to the vaccine development field.

CHALLENGES

There was a gap from vaccine to vaccination. Several challenges have been noted, from vaccine development to vaccination. Vaccine distribution and accessibility were significant global challenges, especially in low- and middle-income countries (LMICs). Another problem is the affordability of vaccine cost and accessibility in LMICs. The vaccine produced should be widely deployed in local communities. In general, developed vaccines usually suffer from underinvestment. However, due to the pandemic, non-profit organizations and governments have financed clinical trials. They invested in expanding vaccine production capacity and building new production facilities. Every country has tried to develop distribution networks. Everybody is focused on facilitating the rapid and successful vaccine roll-out.

LMICs are facing huge financial hurdles. Therefore, sustainable financing and a proper mechanism should be needed to support vaccine production, distribution, and affordability for the LMICs. Strategies should be developed to address these issues adequately for LMICs, which can support future pandemics. Establishing manufacturing capacity and technical expertise is essential for LMICs. To this end, coordinated global steps with adequate funding are required for LMICs.[176] Vaccine logistical problems, such as the cold chain requirement, were significant challenges in vaccine distribution in the LMICs. A lack of a cold chain might hinder vaccine distribution in rural areas of the LMICs.

Other than the logistical and administrative challenges, there are significant changes for LMICs. There are some barriers to vaccination for LMICs. Identifying individuals with priority, such as older patients and patients with disabilities, is one of the critical issues. In this direction, important issues, such as invitations, sending, arranging transport, etc., must be fixed for vaccination. Vaccine hesitancy is prevalent in HICs and LMICs found in all ethnic and socioeconomic groups. All the issues related to vaccine hesitancy should be mitigated.[176]

Overall, purchasing, supply chain management, cold chain transport, vaccine distribution in different parts of the country, and vaccine administration were significant challenges in the LMICs. Providing children with vaccination against COVID-19 was another challenge due to a need for more data.[177] There was an immediate need to develop the COVID-19 vaccine safety and efficacy data for children.

Vaccine safety issues were a concern following COVID-19 vaccination, as were complications reported such as thrombocytopenia, myocarditis or pericarditis, vaccine allergy, etc. For all vaccines, long-term surveillance of safety issues is necessary. HICs, such as the UK, the EU, the USA, Canada, and Australia, have conducted safe surveillance of vaccines. On the other hand, the data on vaccine safety in LMICs remains limited. Very few reports are available for these regions. Therefore, it is necessary to perform surveillance on vaccine safety in LMICs to understand the vaccine safety in these regions.[178] It is necessary to address the vaccine safety concerns through mitigating strategies. There was a call for COVID-19 vaccine modifications in this direction due to safety issues. Another challenge was that reinfection with different variants or subvariants had been reported occasionally.[113,179] Very little data have demonstrated how many booster dosages are needed to prevent reinfection. Ultimately, we need to enhance the surveillance in different aspects of vaccine vaccinations to understand better.

LESSONS LEARNED THAT COULD INFORM PREPAREDNESS FOR FUTURE PANDEMICS

During the COVID-19 pandemic, the health and economic impact was immense; it could have been worse without any modern technology. If we look at other pandemics, between 1346 and 1353, about 200 million individuals died during the plague (bubonic plague). On the other hand, during the 1918 influenza pandemic, about 50 million people died. Therefore, modern technology has been dramatically supported during the pandemic.[180,181] We have learned several lessons from this pandemic, which will help us fight against the next pandemic. First, a lesson we learned was the quick development of vaccines. This rapid introduction of vaccines reduces morbidity and mortality. Rapid vaccine development was possible due to the priority provided to early-stage R&D and vaccine platform technologies. The novel platforms with next-generation technologies for vaccine development, such as mRNA and adenovirus platforms, were noted as the fastest platforms. These novel vaccine technologies have an immense benefit, which help in the next pandemic. mRNA platform depends on the "plug and play." It might help to develop the vaccine in the next pandemic.

Second, adequate manufacturing capacity for new vaccines is essential for rapid and sustainable vaccine development. During the early COVID-19 pandemic, the capacity to manufacture vaccines to fulfill the demand was insufficient.[182] However, manufacturers have scaled up to an exceptional vaccine manufacturing capacity since 2020. By the end of 2021, the International Federation of Pharmaceutical Manufacturers and Associations indicated that vaccine manufacturing capacity worldwide attained about

12.5 billion and, by 2022, it touched 20 billion.[181,183] The increased vaccine manufacturing capacity vaccine might help in the next pandemic.

Third, there was previously a lack of regulatory harmonization, which slowed procurement and trade due to regulatory barriers. It finally hampers the movement of vaccines from procurement to distribution. The urgent need for vaccine distribution during the pandemic streamlined the trade, regulatory, and procurement barriers. Normalized regulatory processes might help prevent the next pandemic.

Fourth, vaccine distribution, surveillance, and monitoring are important factors. Every country's authority has developed a vaccine distribution, surveillance, and monitoring system. Every country monitors swift distribution, vaccination, and safety issues. This surveillance system will help fight against the next pandemic.

Fifth, Omicron is the most transmissible variant, escaping most vaccines. After Omicron, several subvariants were created, escaping most vaccines. Therefore, there was a demand for a universal vaccine that could protect against all the variants and subvariants. On the other hand, several complications were reported after the vaccination, such as thrombocytopenia and myocarditis. Therefore, there was a demand for vaccine modification.

Sixth, we have developed an excellent surveillance system of pathogens using computer science or modern systems and technologies, which may be described as the surveillance of pathogens using intelligence. Now, it is known as pathogen intelligence, an expanded global surveillance system from local-, national-, and international-level data. In low- and middle-income countries, the surveillance is done with community-based and national and global surveillance hubs. It makes the surveillance more robust. Now, the WHO has launched the Hub for Pandemic and Epidemic Intelligence. It will help in the early detection of emerging infectious diseases. This system might help in the early detection of pathogens and the next pandemic.[184,185]

Seventh, collaborative efforts during the pandemic were among the most significant factors in vaccine development and other areas. These collaborations helped to accelerate vaccine development. Different collaborations, such as national, international, industry-academia, industry-academic, and cross-sector collaboration, help with emergency response during pandemics for vaccine R&D and clinical trials. Academic collaboration was one of the most effective collaborations. However, exceptional collaboration has been noted at all levels. It has shown that collaboration can overcome all the health system challenges. Different models are considered during the pandemic, including the ACTIV collaboration for therapeutic and vaccine development and the CovidSurg collaboration to safeguard surgical patients during COVID-19, which can be considered successful models for future pandemics.

ONLY THE END OF THE BEGINNING AND MORE MILES TO GO

Although the COVID-19 vaccine has been developed, every country has completed the vaccination drive. The global acceptability of vaccines varies from country to country. It was very high in China, about 90%, and low in Russia, about 55%.[113,186] Due to the escape mutations of variants and subvariants, vaccines have become less effective.[135] Everybody noted the vaccine escaped the Omicron and its subvariants.[52,136,187] Researchers demanded universal vaccine development against the variant and subvariants. However, universal vaccine development is a significant challenge.[188] Previously, we also urged mutation-proof and next-generation vaccines to fight against the variant and subvariants.[189] In this line, we developed mutation-proof and next-generation vaccines to fight against the variants and subvariants using AI and ML approaches. In this study, we used AI to select the significant mutations in RBD. On the other hand, we used an ML-based approach for immune simulation.[1,190] A vaccine is an essential tool for fighting against the virus. However, an effective and safe vaccine is necessary for complete protection against the virus. On the other hand, motivation is critical to achieve high vaccine uptake. Government and other agencies should work in this direction.

CONCLUSION

The sudden emergence of a highly contagious and previously unknown virus created a global pandemic. The COVID-19 vaccine was developed within a year to fight against the pandemic. However, it was the first time a vaccine was developed within a year, although there were enormous difficulties due to the pandemic. Vaccine researchers have contributed to the development of vaccines and immunity, often working silently. On the other hand, the robust vaccine manufacturing capability was developed during the COVID-19 pandemic which will help to prevent future pandemics.

All lessons were presented for COVID-19 vaccine (R&D) during the pandemic. The most important lesson was learned from strategic PPP collaborations, including the ACTIV model. This model might be considered the best PPP and can be considered for future pandemics.

Several vaccines were periodically developed to fight against the virus during the pandemic. However, during vaccine development and to fight against the pandemic, the public health bodies, governments, vaccine developers, policymakers, regulatory bodies, and funders need to align more. It is time to explore the lessons learned and prepare for global preparedness and agreements for future pandemics. The lessons learned during the pandemic and vaccine development will support us to combat future pandemics.

The pandemics have offered us mRNA technology. Conversely, we found that different variants of SARS-CoV-2 and different subvariants of Omicron have been emerged, from time to time, which are responsible for partial vaccine escape. This mRNA technology might help to develop a universal vaccine considering all variants

of SARS-CoV-2. On the other hand, the potential mRNA technology can also help to develop vaccines for other infectious diseases, which might help us to fight against the future pandemic.

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AUTHOR CONTRIBUTIONS

C.C. did the conceptualization, analysis, software, methodology, writing of the original draft, data curation, supervision of the whole project administration,. Y.-H.L. performed the manuscript validation, formal analysis, and fund acquisition. M.B. did the manuscript visualization, validation, figure and table preparation along with the formal analysis. A.D. carried out the final manuscript draft validation and formal analysis. Z.-H.W. did the validation and formal analysis.

DECLARATION OF INTERESTS

The authors declare no competing interests.

SUPPLEMENTAL INFORMATION

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