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Translational virology: COVID-19, the perfect example

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Abstract

Translational virology, characterized as "from bench to bedside," encompasses all stages from basic research through clinical evaluation and final registration and drug/vaccine approval. The objectives are to accelerate and streamline the innovation process at all stages. It includes identifying disease causes; screening prophylactic and therapeutic candidates; evaluating them in preclinical models and clinical trials; and addressing manufacture, distribution, regulatory review, and authorization. The recent coronavirus disease 2019 (COVID-19) pandemic represents a perfect example of translational virology, demonstrating unprecedented cooperation from the identification of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to the rapid development of potential repurposed and novel drugs, monoclonal antibodies, and vaccines for both prophylactic and therapeutic applications. After confirmation of therapeutic and prophylactic efficacy in animal models, phase I–III clinical trials were conducted with partially overlapping timelines, thereby significantly reducing development time. Both drugs and monoclonal antibodies have been approved for the treatment of patients with COVID-19. Convalescent plasma, mainly used in immunocompromised patients, has been suggested to provide potential benefits. Vaccines based on whole viruses, protein and peptide subunits, viral vectors, and nucleic acids were developed in parallel. Based on good safety profiles and robust immune responses, COVID-19 vaccine candidates were granted emergency use authorization worldwide, enabling mass vaccination. More than 13.6 billion COVID-19 vaccine doses have been administered, and although severe adverse events have been registered, millions of lives have been saved. Due to emerging SARS-CoV-2 variants, vaccine re-engineering has been required as part of translational virology. Vaccine production, storage, transport, and distribution have also been given attention.

Keywords: Basic research; Vaccines; Drugs; Monoclonal antibodies; COVID-19; Clinical trials; SARS-CoV-2 variants; Re-engineered vaccines

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1. Introduction

The objectives of translational research include accelerating the translation of basic research into applied science and innovation, thereby enabling more rapid development of new technologies.[1] The dynamics of translation are complex, systemic, transdisciplinary, inter-institutional, and international. Translational research has received increasing attention recently in the context of drug and vaccine development. It has become

a platform that connects all stages of development, from basic research to the approved end product. It has commonly been defined as "from bench to bedside," implying the steps from basic research to the identification of prophylactic and/or therapeutic compounds/molecules for clinical use in patient care. Moreover, it has been defined as the translation of laboratory findings into real-world applications to enhance patient care and public health. The process is complex and lengthy, involving multiple stages and milestones that must be met before moving forward to the next step. Despite major developments in drug screening and evaluation methods, it is estimated that 90% of clinical drug development still fails.[2]

Translational virology focuses on agents that cause viral diseases, including identification and diagnostics, antiviral drugs, and vaccine development and evaluation in animal models before clinical trials in humans. After confirmation of safety and efficacy in clinical settings, drug/vaccine registration and approval can be received by the authorities. Drug/vaccine production, storage, distribution, and administration are additional important factors. The main drawbacks are the long duration of the whole process and inefficient coordination of the different stages. The coronavirus disease 2019 (COVID-19) pandemic has elevated the whole field of translational virology to a totally new level. Therefore, COVID-19 and especially the unprecedented development of safe and effective vaccines in an impressively short time can be considered a perfect example of translational medicine (Figure 1). Here, perspectives are presented on what has been achieved, what has been learned, and what could have been done differently in hindsight in the development of drugs, monoclonal antibodies, and vaccines at the preclinical and clinical levels. These include issues related to safety and effectiveness, which have been significantly affected by the emergence of numerous severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants. Production, distribution, and administration issues have also been described. Given the broad scope to cover, the field of diagnostics is of great importance; however, the long-term consequences of COVID-19 and the management of individuals with pre-existing conditions are not discussed here. For the literature search, PubMed, Scopus, and Google Scholar were used.

2. Basic research on severe acute respiratory syndrome coronavirus 2

2.1. Identification of infectious agents

The SARS-CoV-2 outbreak struck the world at the end of 2019 and quickly spread, reaching pandemic proportions in March 2020.[3] The first task was to determine the infectious agent causing the outbreak, its source, and route of infection.[4] Relatively quickly, the genetic composition of SARS-CoV-2 was outlined thanks to rapid state-of-the-art next-generation sequencing technologies.[5] SARS-CoV-2

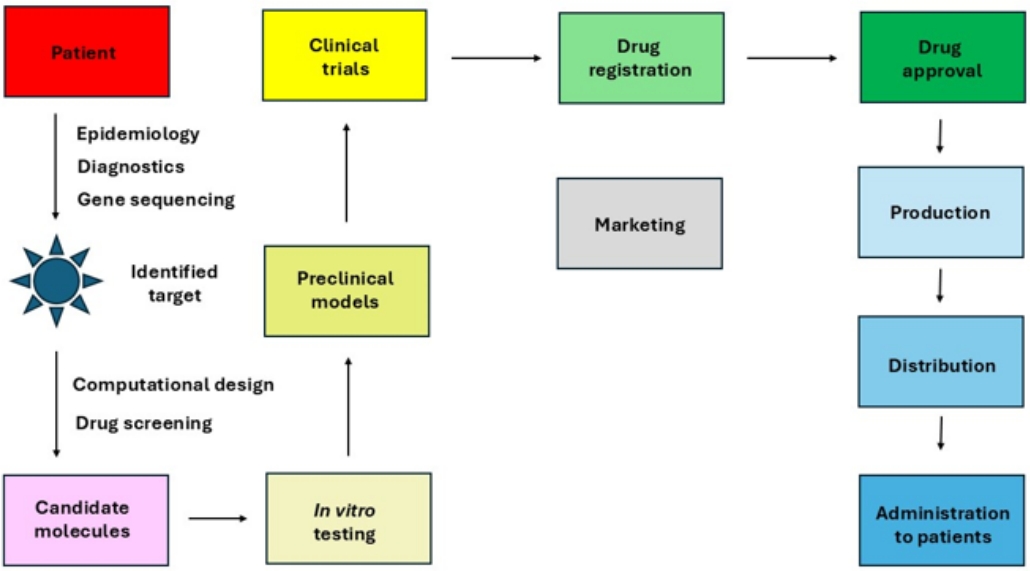

Figure 1. Drug/vaccine development flow chart. The figure illustrates the process from patient diagnosis through target identification and development, approval, and drug/vaccine administration

was quickly identified as a novel human coronavirus, and sequence data provided the necessary information for computational and modeling studies on potential antiviral drugs and vaccines against the virus. Structural studies on whole SARS-CoV-2 particles and individual proteins have also contributed to their identification as potential therapeutic targets.[6]

2.2. Origin of severe acute respiratory syndrome coronavirus 2

Determining the origin of SARS-CoV-2 has been important for better understanding how it could spread so quickly worldwide.[7] Two contradictory theories have been proposed: that SARS-CoV-2 was accidentally released by spillover from a laboratory at the Wuhan Institute of Virology in China or alternatively spread through human contact with zoonotic diseases at a seafood market in Wuhan.

3. Strategies for drug and vaccine development

The global spread of COVID-19 to all corners of the world, resulting in millions of deaths, social suffering, and economic hardships, demanded investment in all possible alternatives to develop prophylactic and therapeutic means for the global population. In this context, enormous resources were dedicated to parallel development of antiviral drugs and vaccines.

3.1. Drugs for Coronavirus Disease 2019

In antiviral drug development, repurposing existing antivirals against other viral diseases has represented the first option for potential targets[8,9] (Table 1). Drug repurposing encompasses approved, investigational, and discontinued drugs and offers several advantages, including prior knowledge of formulation, pharmacology, pharmacokinetics, toxicity, and manufacturing. Moreover, the drug approval process can be shortened, thereby reducing costs. The two types of repurposed drugs for COVID-19 are virus-based and host-focused.[10] Among virus-based repurposed drugs, remdesivir, an RNA-dependent RNA polymerase (RdRp) inhibitor, was effective in hospitalized adults according to a systematic review and meta-analysis.[11] Hospitalized COVID-19 patients who received remdesivir demonstrated a significant survival benefit independent of disease severity.

Favipiravir, another RdRp inhibitor, showed shortened recovery time in surviving COVID-19 patients and significantly reduced 28-day mortality risks in patients with severe disease.[12] In the case of the RdRp inhibitor molnupiravir, little to no difference in all-cause mortality, hospitalization rates, and symptom resolution was demonstrated in outpatients with mild-to-moderate COVID-19 based on 11 studies with 31,272 participants.[13] Paxlovid, the combination of the 3C-protease inhibitor nirmatrelvir and the boosting agent ritonavir,[14] showed significant differences in hospitalization and all-cause mortality compared to the control group in a systematic review and meta-analysis.[15] Moreover, Paxlovid reduced the hospital stay significantly.

Although initially considered a potentially attractive repurposed drug, hydroxychloroquine, previously used for malaria treatment, did not demonstrate significant beneficial therapeutic efficacy against COVID-19 *in vitro*, in animal models, or in clinical trials.[16] Similarly, despite numerous studies on ivermectin, a drug used against parasitic worms, there is low- to high-certainty evidence that it has no beneficial effect in COVID-19 patients.[17] Moreover, there is no evidence that ivermectin can prevent SARS-CoV-2 infections. Unfortunately, ivermectin has

Table 1. Examples of drugs evaluated for COVID-19

Drug	Mechanism	Target population	Outcome
Remdesivir	RdRp inhibitor	Hospitalized	Significant survival benefit[11]
Favipiravir	RdRp inhibitor	COVID-19 patients	Reduced mortality, shortened recovery time[12]
Molnupiravir	RdRp inhibitor	Hospitalized, outpatients	Little/no difference in hospitalization rates, symptom resolution in outpatients[13]
Paxlovid	3C protease inhibitor	Hospitalized	Reduced hospitalization and mortality[14,15]
HCQ	Immunomodulatory	COVID-19 patients	No beneficial effects in animals or humans[16]
Ivermectin	Binding to ion channels	COVID-19 patients	No benefit to COVID-19 patients[17]

Abbreviations: COVID-19: Coronavirus disease 2019; HCQ: Hydroxychloroquine; RdRp: RNA-dependent RNA polymerase.

been associated with two scandals.[18] In an experimental study, ivermectin was distributed to residents with COVID-19 in Mexico City without proper consent or appropriate ethical protections. In another experimental study in a jail in Arkansas, United States, individuals developed serious side effects after receiving high doses of ivermectin without their knowledge.

3.2. Monoclonal antibodies against coronavirus disease 2019

Monoclonal antibodies (mAbs) have proven useful for the treatment of COVID-19 (Table 2). Initially, mAbs against SARS-CoV, such as CR3022, showed potent binding to SARS-CoV-2.[19] The human 47D11 mAb elicited neutralizing antibodies against both SARS-CoV and SARS-CoV-2 S proteins and potent inhibition of Vero E6 cell growth after infection with pseudotyped vesicular stomatitis virus expressing SARS-CoV-2 S protein.[20] Moreover, the S309 mAb from a severe acute respiratory syndrome (SARS) patient neutralized SARS-CoV-2.[21] Interim results from a phase II/III trial with the VIR-7831 mAb (sotrovimab), a modified version of S309 with better half-life, showed reduced risk of progression of mild-to-moderate COVID-19 in high-risk patients.[22] Sotrovimab was granted emergency use authorization (EUA) in the United States in May 2021 and full approval in the European Union for adolescents and adults at high risk of progression to severe COVID-19.[23]

In another approach, the fully humanized neutralizing IgG1 mAb LY-CoV555 (bamlanivimab) demonstrated good safety and tolerability in a phase I study in hospitalized COVID-19 patients.[24] Furthermore, LY-CoV555 has been subjected to monotherapy and in combination with LY-CoV016 (etesevimab) in phase II/III.[25] LY-CoV555 alone did not reduce viral load compared to placebo. In contrast, the combination of LY-CoV555 and LY-CoV016 significantly reduced viral load. Although granted EUA by the Food and Drug Administration (FDA) for treatment of adult and pediatric patients with mild-to-moderate COVID-19,[26] both LY-CoV555 and LY-CoV016 distribution was terminated because they provided no efficacy against COVID-19 variants.[27]

The combination of REGN10987 (imdevimab) and REGN10933 (casirivimab) mAbs targeting different epitopes of the SARS-CoV-2 S receptor binding domain (RBD) showed good safety and reduced viral load in COVID-19 patients in phase II/III.[28] The combination therapy was first granted EUA in the United States, followed by India, Canada, Switzerland, the European Union, the United Kingdom, and Australia.[29]

3.3. Convalescent plasma against coronavirus disease 2019

Especially in the early stages of the pandemic, convalescent plasma transfusions were frequently used for COVID-19 treatment[30] (Table 3). The results of a systematic review and meta-analysis of randomized clinical trials showed that convalescent plasma therapy for COVID-19 was associated with a statistically significant reduction in the risk of hospitalization.[31] On the other hand, the treatment did not prolong survival or improve clinical outcome in hospitalized patients. Convalescent plasma transfusions have yielded mixed results. While a systematic review and meta-analysis suggested benefits[32] and another study reported lower mortality[33] in immunocompromised patients, no clinical improvement was observed in critically ill COVID-19 patients, and no conclusions could be drawn regarding benefits in this population.[34] However, convalescent plasma transfused within 6 months after collection from COVID-19 patients showed good safety and no serious adverse events in randomized controlled clinical trials, which resulted in formal approval of convalescent plasma therapy for immunocompromised patients by the FDA in 2024.[35]

Table 2. Examples of monoclonal antibodies against COVID-19

mAb	Mechanism	Target population	Outcome
Sotrovimab	mAb	High-risk patients	Reduced risk of disease progression[22] EUA in the United States, full approval in the European Union[23]
Bamlanivimab	mAb	Hospitalized patients	Good safety and tolerability in phase I[24]
Bamlanivimab + Etesevimab	mAb combination	Hospitalized patients Risk population	Significantly reduced viral load[25] EUA for adult & pediatric patients[26] Terminated due to no efficacy on variants[27]
Imdevimab + Casirivimab	mAb against RBDepitopes	COVID-19 patients	Good safety and reduced viral load in phase II/III[28] EUA granted in the United States, United Kingdom, and European Union[29]

Abbreviations: COVID-19: coronavirus disease 2019; EUA: Emergency use authorization; mAb: Monoclonal antibody; RBD: Receptor-binding domain.

Table 3. Examples of convalescent plasma against COVID-19

Convalescent plasma	Target population	Outcome
Plasma from COVID-19 patients	COVID-19 patients	Statistically lower risk of hospitalization[31]
Plasma from COVID-19 patients	COVID-19 patients	No prolonged survival or improved clinical outcome in hospitalized patients[31]
Plasma from COVID-19 patients	COVID-19 patients	Benefits[32] and lower mortality in immunocompromised patients[33]
Plasma from COVID-19 patients	COVID-19 patients	No improvement in critically ill COVID-19 patients[34] Approval by the FDA in immunocompromised patients[35]

Abbreviations: COVID-19: Coronavirus disease 2019; FDA: Food and Drug Administration.

3.4. Vaccines against COVID-19

The development of COVID-19 vaccines has made a significant contribution to saving millions of lives and has downgraded the pandemic to an epidemic status[36] (Table 4). Due to the available expertise across different vaccine types, COVID-19 vaccines based on whole viruses, protein subunits, viral vectors, and nucleic acids have been developed in parallel.[37] Because of the urgent need, no resources were spared, and timelines were shortened; instead of finalizing preclinical studies before starting clinical trials, overlapping activities were conducted.[38] For example, after briefly confirming COVID-19-specific antibody responses and protection against SARS-CoV-2 challenges in animal models, clinical phase I safety studies were initiated in healthy volunteers. While phase I trials were still in progress, phase II trials were initiated, and, based on positive interim results from phase II, phase III studies commenced. Production of large quantities of vaccine candidates also began early to ensure that sufficient ready-to-use vaccines were available once an EUA was granted for mass vaccination.

In the case of whole-virus vaccines, the CoronaVac (Sinovac) vaccine achieved 50.7% efficacy against symptomatic COVID-19 and 100% efficacy against hospitalization in phase III.[39] CoronaVac was granted EUA in 54 countries in 2021.[40] Another whole-virus vaccine, BBIBP-CorV (Sinopharm), provided 78.1% vaccine efficacy in phase III.[41] BBIBP-CorV received EUA by the World Health Organization in 2021.[42] Protein subunit-based vaccines such as COVAX-19 have elicited robust immunogenicity in phase II study.[43] Moreover, COVAX-19 reduced the severity and rates of COVID-19 in phase III.[44] Nanoparticle-encapsulated full-length SARS-CoV-2 S protein vaccine NVX-CoV2373 showed antibody and $CD4^+$ T-cell responses, which were superior to those seen in convalescent COVID-19 patients in phase I/II.[45] The COVAX-19 vaccine gave 76.3% efficacy against symptomatic COVID-19 and 100% efficacy against severe disease in phase III.[46] Conditional marketing authorization was given to NVX-CoV2373 in the European Union in 2021 and in the United Kingdom in 2022.[47]

A number of viral vectors have been used in the development of COVID-19 vaccines, as previously described.[37] For this reason, only a brief description of the most advanced vaccines developed for adenoviruses is presented here. In this context, the ChAdOx1 nCoV-19 vaccine based on the full-length chimpanzee virus vector ChAdOx1 expressing the full-length SARS-CoV-2 S protein provided 62–90% vaccine efficacy in phase III[48] and received EUA in the United Kingdom in 2020.[49] The Ad5-nCoV vaccine based on the human adenovirus 5 (Ad5) serotype was granted EUA in China in 2021.[50] Another strategy has been to apply a prime-boost regimen, where administration of the SARS-CoV-2 S expressed from an Ad26 is followed by another vaccination with an Ad5-based vector.[51] The Russian Ad26-S/Ad5-S vaccine (Sputnik V) showed a 91.6% vaccine efficacy in phase III.[52] Despite being tested in only 76 volunteers, it controversially received EUA in Russia in 2020.[53] In contrast to the above-described adenovirus-based vaccines, the Ad26.COV2.S vaccine required only a single dose, resulting in 52.9% vaccine efficacy in phase III[54] and FDA EUA in 2021.[55]

Among nucleic acid-based vaccines, the synthetic INO-4800 DNA vaccine elicited robust immune responses in phase II after a booster immunization with 1 or 2 mg of DNA vaccine in persons previously vaccinated twice with INO-4800.[56] Dose-dependent superior immunogenicity was observed with the higher dose. The ZyCoV-D DNA vaccine expressing the SARS-CoV-2 S RBD showed good safety and strong immune responses in phase I/II[57] and a 66% vaccine efficacy in phase III.[58] ZyCoV-D received EUA in India in 2021.[59]

Table 4. Comparison of COVID-19 vaccines

Vaccine	Efficacy	Advantages	Disadvantages
Inactivated CoronaVac BBiBP-CorV	Hospitalization: 100% Symptomatic: 51% 78% efficacy	Not restricted to S protein Broad antigen responses Granted EUA	Time-consuming development Low re-engineering flexibility
Protein COVAX-19 NVX-CoV2373	Severe disease: 78% 44% efficacy Symptomatic: 76% Severe COVID-19: 100%	Easy manipulation, relatively cheap production	Inferior delivery compared to viral vectors and LNP-encapsulated mRNA
Viral vector ChAdOx1 Ad5-nCoV Ad26-COV2.S	62–90% efficacy 92% efficacy	Relatively easy manipulation, Efficient delivery	Potential rare SAEs Safety concerns of viral spread
DNA INO-4800 ZYCOV-D	66% efficacy	Easy manipulation and re-engineering, cheap production	Inferior delivery compared to viral vectors and LNP-encapsulated mRNA Risk of chromosomal integration
RNA BNT162b2 mRNA-1273	95% efficacy 94% efficacy	Easy manipulation and re-engineering	Sensitive to RNA degradation requires LNP-encapsulation Potential rare SAEs

Abbreviations: COVID-19: Coronavirus Disease 2019; EUA: Emergency use authorization; LNP: Lipid nanoparticle; SAEs: Severe adverse events.

Much attention has been paid to RNA-based COVID-19 vaccines. Application of mRNA-based vaccines has presented some challenges. Obviously, the biggest challenge concerns the sensitivity of single-stranded mRNA molecules to degradation. This problem has been addressed through physical, chemical, and biological mechanisms. For example, cation neutralization, modification of secondary structures, introduction of tertiary motifs, and chemical modifications have improved stability. Lipid nanoparticle (LNP) encapsulation has provided protection against degradation and has also improved delivery. The LNP-encapsulated prefusion-stabilized full-length SARS-CoV-2 S RNA (BNT162b2) vaccine demonstrated a 95% vaccine efficacy in phase III,[60] and an EUA was granted in 2020 in the European Union and Switzerland.[61] Similarly, the mRNA-1273 vaccine demonstrated 94.1% efficacy in phase III,[62] and the FDA granted an EUA in 2020.[63] An interesting approach for mRNA-based vaccines has been the use of self-amplifying RNA technology, which has generated higher mRNA levels with lower immunization doses compared to conventional synthetic mRNA.[64] Based on the Venezuelan equine encephalitis virus (VEE) RNA replicon, the LNP–nCoVsaRNA vaccine showed good safety and tolerability in phase I despite not reaching 100% seroconversion rates.[65] In phase II, enhanced seroconversion was achieved by prolonged dose intervals and booster immunizations.[66] Another lipid organic nanoparticle formulation for VEE–SARS-CoV-2 S RNA demonstrated excellent safety and robust immunogenicity in phase II/III[67], and it received EUA in India in 2025.[68]

4. Safety, efficacy and hesitancy

Drug and vaccine safety is essential for any medical intervention. In the context of the COVID-19 pandemic, the main concern has been adverse events, especially after mass vaccinations of generally healthy individuals. Moreover, the effect on persons with pre-existing medical conditions and their reactions to drugs and vaccines need to be considered.

4.1. Drug safety and efficacy

Clinical trials initially provided relevant information on the safety and tolerability of novel COVID-19 drugs. Moreover, drug efficacy has been compared with the standard-of-care treatment to determine whether drug candidates should advance to additional clinical trials and further be considered for drug registration and approval. Case reports also play an important role in the development process. The special case of COVID-19, with its wide spectrum of approaches and drug molecules, has, however, caused issues, as efforts have been wasted on small, underpowered studies for which it has been unclear whether certain drugs can be recommended.[69] It has been estimated that more than 90% of COVID-19 drug studies fall under this category.[70] Despite that, effective drugs are available for the treatment of COVID-19 as discussed earlier.

4.2. Vaccine safety and efficacy

In the case of COVID-19 vaccines, the question of safety has received even greater attention than for drugs. On one hand, vaccinations have always been associated with certain fears, suspicions, and risks, which have reached unprecedented levels with the application of mRNA-based vaccines. On the other hand, the mass vaccination of more than 16 billion doses administered globally has certainly revealed a spectrum of adverse events that would most likely go undetected in smaller-scale vaccination programs.

Generally, all types of COVID-19 vaccines have demonstrated good safety profiles and tolerability. However, serious adverse events have been reported for several premature non-communicable diseases after vaccinations, as reviewed in detail elsewhere.[71] An association was established between COVID-19 vaccination and thromboembolic events.[72] The incidence of Ad26.COV2.S vaccination and thrombocytopenia syndrome (TTS) has been estimated at 3.3 cases per million doses. In the case of cerebral venous thrombosis, the ratio was 1.93 for the ChAdOx1 vaccine. The BNT162b2 vaccine showed a much lower TTS rate of 0.00865 cases per million doses.

In the case of mRNA vaccines, post-vaccine myocarditis has been reported within days and weeks of vaccination.[73] The disease is generally mild but has shown the highest rates in males aged 13 to 39. The incidence of myocarditis after mRNA vaccinations varies between 9 and 80 per million across studies. For example, in one study in Israel, the incidence rate was 6.9 per million for female recipients and 80 per million for males. It is also important to point out that the overall risk of hospitalization and death is substantially higher for SARS-CoV-2-infected individuals than for those with post-vaccine myocarditis.

Although pre-existing medical conditions and genetic predisposition have been linked to post-vaccination adverse events, serious attention and monitoring are required. In any case, vaccinations have saved millions of lives, and the benefits clearly outweigh the risks. Unfortunately, massive misinformation and disinformation have discredited vaccine safety and increased vaccine hesitancy, as discussed later in this review.

The different types of COVID-19 vaccines have also proven effective in significantly reducing hospitalizations, mortality, and symptomatic COVID-19 cases. However, the original COVID-19 vaccines did not protect individuals from SARS-CoV-2 transmission. Moreover, vaccine effectiveness has decreased, which can, to some extent, be explained by the prolonged interval since the last vaccination. Booster vaccinations have therefore indeed enhanced effectiveness.

4.3. Severe acute respiratory syndrome coronavirus 2 variants and vaccine efficacy

Emerging variants of the original SARS-CoV-2 strain have significantly contributed to the reduced vaccine effectiveness.[74] Although not considered a virus with a high mutation frequency,[75] a spectrum of mutations in the SARS-CoV-2 S protein and elsewhere in the genome have been identified. Many SARS-CoV-2 variants, such as Alpha, Beta, Gamma, Delta, and Omicron and their many subvariants, have shown significant reduction in vaccine efficacy.[76] This problem has been addressed by the re-engineering of existing COVID-19 vaccines. For example, the bivalent mRNA-1273.214 vaccine, which contains the original mRNA-1273 and the corresponding RNA for the omicron BA.1 variant, enhanced neutralizing antibody titers against omicron and induced binding activity against the alpha, beta, gamma, and delta variants in phase II/III compared to the mRNA-1273 vaccine.[77] Moreover, booster vaccinations with the re-engineered mRNA XBB.1.5 vaccine elicited 37-fold higher neutralizing antibody titers against the omicron XBB.1.5 and EG.5.1 variants.[78] In a systematic bioinformatics approach, analysis of omicron variants identified a proline-to-leucine substitution in the SARS-CoV-2 S protein, which significantly enhanced S-mediated viral entry and the immunogenicity of mRNA vaccines, providing an alternative for improved vaccine efficacy.[79]

4.4. Vaccine hesitancy

The success of vaccination relies not only on vaccine efficacy but also on consistently high vaccination rates across populations. Although widespread childhood vaccination has eliminated or restricted many infectious diseases such as smallpox, polio, and measles, the recent decline in vaccination rates has increased the risk of their re-emergence. Based on estimates from a modeling study in the United States,[80] declining childhood vaccination rates will most likely increase the frequency and size of outbreaks of such diseases as measles, rubella, poliomyelitis, and diphtheria, making them endemic. Similarly, attacks against polio vaccine campaigns and healthcare workers have taken place in Pakistan and Afghanistan, claiming that the vaccinations only serve Western propaganda and present a serious health risk to the local population.[81]

Skepticism and hesitancy have reached new levels with the COVID-19 pandemic.[71] The use of mRNA-based vaccines, in particular, has raised concerns with claims that the novel mRNA technology has never been tested in animal models and human trials despite publications in the 1990s of safe and successful mRNA delivery to mice[82] and numerous phase I–III trials conducted in humans[37] before EUA was granted. Another issue contributing to

mistrust comprises the adverse events associated with vaccinations. There is no denial of even severe adverse events registered in vaccinated individuals, with an estimated more than 13.6 billion COVID-19 vaccine doses administered globally.[83] However, in many cases only the temporal and not the causal association has been confirmed. Rigorous evidence-based science has, through numerous clinical and epidemiological studies, confirmed that the benefits of COVID-19 vaccinations far outweigh the risks. Unfortunately, much of this information is based on no reliable scientific studies and is rather spread by individuals opposed to any vaccine development. Moreover, irresponsible misinformation and disinformation can be easily shared on social media platforms without any responsibility or consequences.

One factor affecting trust in COVID-19 vaccines is the misunderstanding in the general population that, like vaccines against other respiratory diseases, COVID-19 vaccines do not completely prevent infections. Therefore, as breakthrough infections occurred among vaccinated individuals, it was generally assumed that vaccination was ineffective, thereby reducing willingness to receive COVID-19 vaccination.

Hesitancy toward COVID-19 vaccines has been studied through numerous surveys and systematic reviews. For example, vaccine hesitancy was strongly influenced by sex, age, education level, and income status among Blacks/African Americans.[84] In a Chinese online survey, individuals with higher educational levels, married people, people in good health, non-smokers, and persons who paid attention to hygiene practices such as handwashing, mask-wearing, and social distancing showed a more positive attitude toward COVID-19.[85] Individuals who were less likely to endorse conspiracy theories, but who showed higher levels of trust in medical doctors, were more favorable towards vaccinations. Interestingly, a study of 12–15-year-old children found that 42% showed no hesitancy toward COVID-19 vaccination, 22% "a little hesitancy," 21% "some hesitancy," and 15% "strong hesitancy."[86] Moreover, a correlation between TV watching and hesitancy was established, although factors such as age, gender, race, and parental education were not statistically significant. Based on a meta-analysis of 35 studies, a remarkably large variation was observed among healthcare workers in different countries.[87] A substantially low vaccine hesitancy, at 4.3%, was observed in China, whereas 8%–18% was reported in the United States, 7%–32.5% in Europe, and 72% in Africa. Male healthcare workers, elderly people, and those with doctoral degrees were generally more accepting of vaccination, as were persons who had been infected with SARS-CoV-2, had directly cared for patients, or had experience with influenza vaccinations. Vaccine hesitancy was higher among men, residents in rural areas, parents with children younger than 18 years, and people preferring information from peers, social media, online forums, and blogs in a Norwegian study.[88] Correlation between conspiracy theories and vaccine hesitancy could be demonstrated[89] among individuals who did not consider the COVID-19 pandemic dangerous and who denied the existence of SARS-CoV-2. Typically, individuals who considered COVID-19 vaccines unsafe had less knowledge about SARS-CoV-2/COVID-19, favored myths and conspiracy theories, had lower levels of education, earned less, and lived in rural areas according to a national survey in the United States.[90] According to a recent study in Ireland, the concept of vaccine effectiveness and its waning with time are not well understood by the general public, and these issues need to be addressed.[91] Therefore, access to accurate and science-based information on COVID-19 and the safety and efficacy of existing vaccines is of utmost importance to be able to resist and counteract the massive misinformation and disinformation campaigns.[89]

5. Drug and vaccine production and distribution

Drug production has mainly followed conventional procedures established for drugs targeting infectious diseases. In the case of vaccines, methods based on whole viruses, protein subunits, and viral vectors have already been developed and even utilized for years. However, in the case of whole-virus vaccines, handling live virus and vaccine production require high-level BSL-3 facilities, which are time- and cost-consuming. Handling viral vectors for vaccine development is associated with biosafety concerns that must be addressed throughout the entire production and post-production stages. In the context of RNA-based vaccines, the COVID-19 mRNA vaccines were the first produced in large quantities for mass vaccination, and despite their relatively simple manufacturing process, a well-established platform is still needed to improve production capacity.[92] The initial mRNA-based vaccines were extremely temperature sensitive, requiring their storage and transport at −80 °C,[93] which became a major challenge for mass vaccination in developing countries. Upstream processing comprises enzymatic mRNA synthesis, and downstream processing includes mRNA purification followed by LNP formulation and fill-to-finish steps.[94] In the context of *in vitro* transcription, the methods can be improved by continuous processing, which can have a positive impact on reducing costs and operation time and facilitate automation for higher productivity

and better product quality.[95,96] Furthermore, minimizing expensive reagents can reduce costs.[97] The quantity of the required mRNA dose and the production scale will have a strong impact on the costs of the upstream process. In this context, the application of the saRNA platform, in which 100- to 1,000-fold lower doses than conventional mRNA are needed to induce protective immune responses,[98] is an attractive alternative for cost-effective RNA vaccine production.

Downstream processing remains a bottleneck for cost-effective RNA production. Attention is required for mRNA purification to develop new chromatographic modes to avoid multiple mRNA purification steps. For example, application of multimodal chromatography has provided promising results in an integrated and intensified purification process.[99]

For mRNA products, the freeze-drying process of lyophilized mRNA–LNPs can be optimized by selecting an appropriate buffer and cryoprotectant.[100] This process maintained LNP characteristics and functionality of mRNA vaccines under refrigerated conditions for at least a year, thereby offering a viable solution for mRNA vaccine distribution.

As for other indications, the distribution of novel medications and vaccines is seriously biased for the rich and the developed countries. On the one hand, costs play an important role, but the logistics of delivery and the storage capacity for thermosensitive drugs and vaccines under special conditions also present real challenges. The development of appropriate cold chain storage, logistics, and vaccine management was needed to overcome the pandemic.[101] In another approach, product stability and half-life extension have been achieved by engineering thermostable vaccines, which allow transport and storage under less demanding conditions. For example, thermostable mRNA-based vaccines have successfully been developed.[102,103] In a novel approach, a lipid-free mRNA vaccine was engineered by spray-drying RNA embedded in glassy polysaccharide microparticles followed by atomic layer deposition.[103] The alumina-coated mRNA vaccine could be stored for 6 months at temperatures of 40 °C.

6. Conclusion

Important milestones have now been reached six years after the onset of the COVID-19 pandemic. Translational research has proven essential for the development of biological therapeutics such as mAbs and transfused convalescent plasma from COVID-19 patients. Formal approval of mAbs has been obtained for the treatment of individuals at high risk of developing severe COVID-19.[23] Moreover, convalescent plasma transfusions for immunocompromised individuals have received full FDA approval.[35] However, despite some success, the development of chemical drugs for COVID-19 has been less efficient and the utilization of translational research less prominent. Undoubtedly, major progress in this field has been achieved, leading to the approval of vaccines for global use. Particularly, mass vaccinations have substantially contributed to the downgrading of COVID-19 to an endemic status and allowed society to open to normal activities after the unprecedented lockdown experienced in many countries. The success can be attributed in part to translational virology, which enabled exceptionally rapid development of drugs and vaccines, thereby preventing asymptomatic COVID-19 and particularly reducing hospitalization and mortality rates. Unfortunately, unfounded and unscientific activities directed against researchers, clinicians, authorities, pharmaceutical, and biotechnology companies tried not only to question the safety and efficacy of vaccines but also claimed that the COVID-19 pandemic was intentionally engineered and that the vaccines were developed as bioweapons.[104] Conspiracy theories went so far claiming that vaccines contained microchips to control individuals.[105] Fortunately, the reality based on sound scientific observations from large clinical trials and epidemiologic reports has confirmed the high efficacy and solid safety of COVID-19 vaccines. However, the continued emergence of SARS-CoV-2 variants that have reduced the effectiveness of COVID-19 vaccines has necessitated accelerating booster vaccinations and re-engineering of existing vaccines. It has also encouraged the development of novel vaccines targeting conserved regions of the SARS-CoV-2 genome that are less prone to mutation.[106] The recombinant full-length-based N-protein vaccine showed a favorable safety profile and significant efficacy in a phase III trial.[106] Another area to explore is the route of vaccine administration to further optimize delivery and immune responses. In this context, given the respiratory nature of SARS-CoV-2 infections, intranasal administration has proven superior to conventional intramuscular administration[107] and warrants further exploration. In any case, as the translational research platforms are well established, their use will substantially accelerate success.

A comparison of the COVID-19 pandemic with the previous SARS epidemic revealed a major difference in disease presentation. SARS never reached pandemic proportions with total cases of 8,422, 916 deaths, and a case fatality rate of 11%.[108] In contrast, more than 780 million cases have been reported for COVID-19, causing more than 7.1 million deaths and case fatality rates varying

with age being 0.015% (0–17 years), 0.15% (18–49 years), 2.3% (50–74 years), 17% (75 years or over).[83] A remarkable difference between SARS and COVID-19 is that while SARS surprisingly ended,[109] COVID-19 continues its presence in an endemic state. The reason for this is unclear. In any case, SARS-CoV-2 remains widespread, and emerging variants continue to appear (Figure 2).

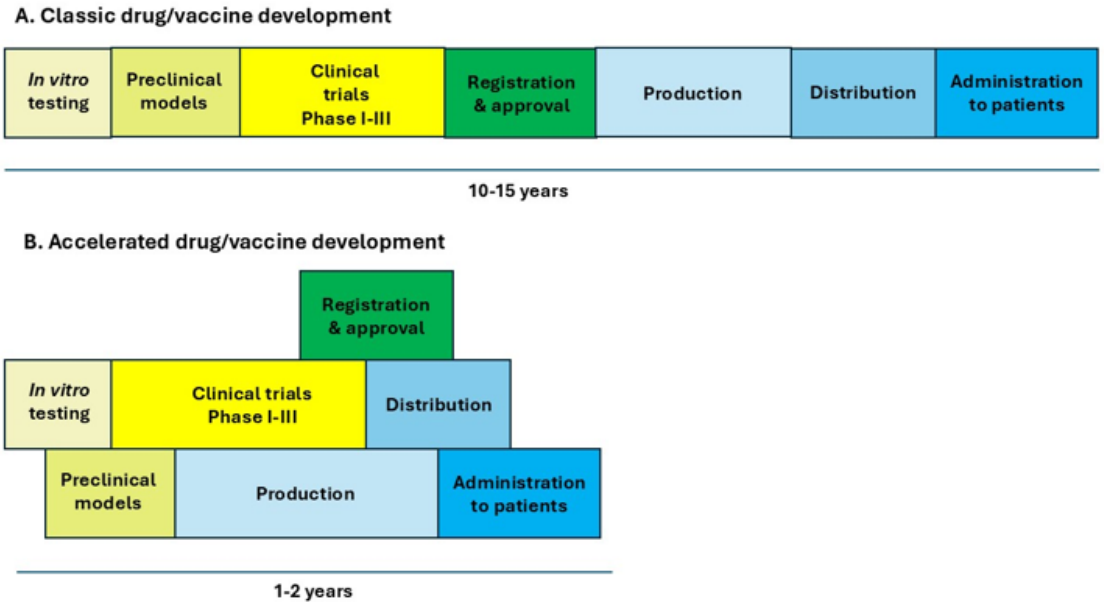

Figure 2. Timelines for drug/vaccine development. Illustration of timelines for classic drug/vaccine development (A) compared to accelerated drug/vaccine development (B).

7. Lessons learned for future pandemics

Today, despite all efforts, COVID-19 has not yet been eradicated and requires vigilance to act quickly in case of the emergence of extraordinary SARS-CoV-2 variants or other infectious pathogens. It is therefore important to stay alert and apply the expertise acquired across the various stages of translational virology during the COVID-19 pandemic in the case of another outbreak. Epidemiologic monitoring, outbreak surveillance, and rapid and accurate diagnostic capacity are essential assets. Moreover, all the accumulated expertise and know-how in drug and vaccine development put us in a much more favorable position compared to the pre-COVID-19 situation. In particular, the long-awaited emergence of mRNA-based vaccines and the highly promising use of self-amplifying RNA will enhance confidence in the ability to quickly prevent the global spread of future pathogens. Moreover, the accelerated development of COVID-19 vaccines significantly reduced the overall process duration, and the approach can be directly applied to other infectious diseases.

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The author declares that there are no competing interests or conflicts of interest.

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References

1. Mayrink NN, Alcoforado L, Chioro A, *et al.* Translational research in health technologies: A scoping review. *Front Digit Health*. 2022;4:957367.

   doi: 10.3389/fdgth.2022.957367

2. Sun D, Gao W, Hu H, Zhou S. Why 90% of clinical drug development fails and how to improve it? *Acta Pharm Sinica B*. 2022;12(7):3049-3062.

   doi: 10.1016/j.apsb.2022.02.002

3. Das K, Pingali MS, Paital B, *et al.* A detailed review of the outbreak of COVID-19. *Front Biosci*. 2021;26(6):149-170.

   doi: 10.52586/4931

4. Mohamadian M, Chiti H, Shoghli A, Biglari S, Parsamanesh N, Esmaeilzadeh A. COVID-19: Virology, biology and novel laboratory diagnosis. *J Gene Med*. 2021;23(2):e3303.

   doi: 10.1002/jgm.3303

5. Naqvi AA, Fatima K, Mohammad T, *et al.* Insights into SARS-CoV-2 genome, structure, evolution, pathogenesis and therapies: structural genomics approach. *Biochim Biophys Act Mol Basis Dis.* 2020;1866(10):165878.

   doi: 10.1016/j.bbadis.2020.165878

6. Yang H, Rao Z. Structural biology of SARS-CoV-2 and implications for therapeutic development. *Nat Rev Microbiol*. 2021;19(11):685-700.

   doi: 10.1038/s41579-021-00630-8

7. Hao YJ, Wang YL, Wang MY, *et al.* The origins of COVID-19 pandemic: A brief overview. *Transbound Emerg Dis*. 2022;69(6):3181-3197.

   doi: 10.1111/tbed.14732

8. De P, Chakraborty I, Karna B, Mazumder N. Brief review on repurposed drugs and vaccines for possible treatment of COVID-19. *Eur J Pharmacol*. 2021;898:173977.

   doi: 10.1016/j.ejphar.2021.173977

9. Kushwaha ND, Mohan J, Kushwaha B, *et al.* A comprehensive review on the global efforts on vaccines and repurposed drugs for combating COVID-19. *Eur J Med Chem*. 2023;260:115719.

   doi: 10.1016/j.ejmech.2023.115719

10. Saul S, Einav S. Old drugs for a new virus: repurposed approaches for combating COVID-19. *ACS Infect Dis*. 2020;6(9):2304-2318.

    doi: 10.1021/acsinfecdis.0c00343

11. Bartoletti M, Mozaffari E, Amin AN, *et al.* A Systematic Review and Meta-analysis of the Effectiveness of Remdesivir to Treat SARS-CoV-2 in Hospitalized Patients: Have the Guidelines Evolved with the Evidence? *Clin Infect Dis*. 2025;81(1):20-29.

    doi: 10.1093/cid/ciaf111

12. Srisubat A, Thanasitthichai S, Kongsaengdao S, Maneeton N, Maneeton B, Akksilp S. Effectiveness of Favipiravir monotherapy in the treatment of COVID-19: real world data analysis from Thailand. *Lancet*. 2023;11:100166.

    doi: 10.1016/j.lansea.2023.100166

13. Tatz GS, Ochodo EA, Fox T, *et al.* Molnupiravir for treating COVID-19. *Cochrane Database Syst Rev*. 2025;10(10):CD015381.

    doi: 10.1002/14651858.CD015381.pub2

14. Singh RSP, Toussi SS, Hackman F, *et al.* Innovative randomized phase I study and dosing regimen selection to accelerate and inform pivotal COVID-19 trial of nirmatrelvir. *Clin Pharmacol Therapeut*. 2022;112(1):101-111.

    doi: 10.1002/cpt.2603

15. Wang Y, Yang Y, Shan R, Zhao L, Bai Y, Feng, L. Paxlovid for the treatment of COVID-19: a systematic review and meta-analysis. *J Infect Dev Ctries*. 2024;18(8):1169-1178.

    doi: 10.3855/jidc.19202

16. Chen Y, Li MX, Lu GD, Shen HM, Zhou J. Hydroxychloroquine/Chloroquine as Therapeutics for COVID-19: Truth under the Mystery. *Int J Biol Sci*. 2021:17(6):1538-1546.

    doi: 10.7150/ijbs.59547

17. Popp M, Reis S, Schießer S, *et al.* Ivermectin for preventing and treating COVID-19. *Cochrane Database Syst Rev.* 2022;6(6):CD015017.

    doi: 10.1002/14651858.CD015017.pub3

18. Meyerowitz-Katz G, Wieten S, de Jesus Medina Arellano M, Yamey G. Unethical studies of ivermectin for COVID-19. *BMJ*. 2022;377:0917.

    doi: 10.1136/bmj.o917

19. Tian X, Li C, Huang A, *et al.* Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody. *Emerg Microbes Infect*. 2019;9(1):382-385.

    doi: 10.1080/22221751.2020.1729069

20. Wang C, Li W, Drabek D, *et al.* A human monoclonal antibody blocking SARS-CoV-2 infection. *Nat Commun*. 2020;11(1):2251.

    doi: 10.1038/s41467-020-16256-y

21. Pinto D, Park Y-J, Beltramello M, *et al.* Cross-neutralization of SARS- CoV-2 by a human monoclonal SARS-CoV antibody. *Nature*. 2020;583(7815):290-295.

doi: 10.1038/s41586-020-2349-y

22. Gupta A, Gonzalez-Rojas Y, Juarez E, *et al.* Early Treatment for Covid-19 with SARS-CoV-2 Neutralizing Antibody Sotrovimab. *N Engl J Med*. 2022;385(21):1941-1950.

doi: 10.1056/NEJMoa2107934

23. Heo Y-A. Sotrovimab: First Approval. *Drugs*. 2022;82(4):477-482.

doi: 10.1007/s40265-022-01690-7

24. Tuccori M, Ferraro S, Convertino I, *et al.* Anti-SARS-CoV-2 neutralizing monoclonal antibodies: clinical pipeline. *Mabs*. 2020;12(1):1854149.

doi: 10.1080/19420862.2020.1854149

25. Gottlieb, R.L., Nirula, A., Chen, P., Boscia, J., Heller, B., Morris, J., *et al.* Effect of Bamlanivimab as monotherapy or in combination with Etesevimab on viral load in patients with mild to moderate COVID-19: a randomized clinical trial. *JAMA*. 2021;325(7):632-644.

doi: 10.1001/jama.2021.0202

26. U.S. Food and Drug Administration. Coronavirus (COVID-19) Update: FDA Authorizes Monoclonal Antibodies for Treatment of COVID-19. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibodies-treatment-covid-19-0

27. Drugs and Lactation Database (LactMed®). Etesevimab and Bamlanivimab. Bethesda (MD): National Institute of Child Health and Human Development; 2023.

28. Weinreich DM, Sivapalasingam S, Norton T, *et al.* REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. *N Engl J Med*. 2021;384(3):238-251.

doi: 10.1056/NEJMoa2035002

29. Deeks ED. Casirivimab/Imdevimab; First Approval. *Drugs*. 2021;81(17):2047-2055.

doi: 10.1007/s40265-021-01620-z

30. Rajendran K, Krishnasamy N, Rangarajan J, Rathinam J, Natarajan M, Ramachandran A. Convalescent plasma transfusion for the treatment of COVID-19: Systemic review. *J Med Virol*. 2020;92(9):1475-1483.

doi: 10.1002/jmv.25961

31. Filippatos C, Ntanasis-Stathopoulos I, Sekeri K, *et al.* Convalescent Plasma Therapy for COVID-19: A Systematic Review and Meta-Analysis on Randomized Controlled Trials. *Viruses*. 2023;15(3):765.

doi: 10.3390/v15030765

32. Nissen-Meyer LSH, Macpherson ME, Skeie LG, *et al.* COVID-19 patients treated with convalescent plasma. *Tidsskr Nor Laegeforen*. 2023;143(11).

doi: 10.4045/tidsskr.22.0577

33. Senefeld JW, Franchini M, Mengoli C, *et al.* COVID-19 Convalescent Plasma for the Treatment of Immunocompromised Patients: A Systematic Review and Meta-analysis. *JAMA Netw Open*. 2023;6(1):e2250647.

doi: 10.1001/jamanetworkopen.2022.50647

34. Beraud M, Goodhue Meyer E, Lozano M, Bah A, Vassallo R, Brown BL. Lessons learned from the use of convalescent plasma for the treatment of COVID-19 and specific considerations for immunocompromised patients. *Transfus Apher Sci*. 2022;61(3):103355.

doi: 10.1016/j.transci.2022.103355

35. Sullivan DJ, Reik R, Prichard A, *et al.* COVID-19 plasma safety and efficacy analysis for biological license application approval. *Exp Rev Anti Infect Ther*. 2026;24(1):97-111.

doi: 10.1080/14787210.2026.2623136

36. Biancolella M, Colona VL, Mehrian-Shai R, *et al.* COVID-19 2022 update: Transition of the pandemic to the endemic phase. *Hum Genomics*. 2022;16(1):19.

doi: 10.1186/s40246-022-00392-1

37. Lundstrom K. COVID-19 Vaccines: Where Did We Stand at the End of 2023? *Viruses*. 2024;16(2):203.

doi: 10.3390/v16020203

38. Krammer F. SARS-CoV-2 vaccines in development. *Nature*. 2020;586(7830):516-527.

doi: 10.1038/s41586-020-2798-3

39. Palacios R, Patiño EG, de Oliveira Piorelli R, *et al.* Double-Blind, Randomized, Placebo-Controlled Phase III Clinical Trial to Evaluate the Efficacy and Safety of treating Healthcare Professionals with the Adsorbed COVID-19 (Inactivated) Vaccine Manufactured by Sinovac—PROFISCOV: A structured summary of a study protocol for a randomized controlled trial. *Trials*. 2020;21(1):853.

doi: 10.1186/s13063-020-04775-4

40. World Health Organization. The WHO Validates Sinovac COVID-19 Vaccine for Emergency Use and Issues Interim Policy Recommendations. 2021. Accessed April 23, 2026. https://www.who.int/news/item/01-06-2021-who-validates-sinovac-covid-19-vaccine-for-emergency-use-and-issues-interim-policy-recommendations

41. Al Kaabi N, Zhang Y, Xia S, *et al.* Effect of 2 Inactivated SARS-CoV-2 Vaccines on Symptomatic COVID-19 Infection in Adults: A Randomized Clinical Trial. *JAMA*. 2021;326(1):35-45.

doi: 10.1001/jama.2021.8565

42. Taylor A. WHO Grants Emergency Use Authorization for Chinese-Made Sinopharm Coronavirus Vaccine. The Washington 2021. Accessed April 23, 2026. https://www.washingtonpost.com/world/2021/05/07/who-sinopharm-emergency-use/

43. Tabarsi P, Anjidani N, Shahpari R, *et al.* Safety and

immunogenicity of SpikoGen®, an Advax-CpG55.2-adjuvanted SARS-CoV-2 spike protein vaccine: A phase 2 randomized placebo-controlled trial in both seropositive and seronegative populations. *Clin Microbiol Infect*. 2022;28(9):1263-1271.

doi: 10.1016/j.cmi.2022.04.004

44. Tabarsi P, Anjidani N, Shahpari R, *et al.*, Evaluating the efficacy and safety of SpikoGen®, an Advax-CpG55.2-adjuvanted severe acute respiratory syndrome coronavirus 2 spike protein vaccine: A phase 3 randomized placebo-controlled trial. *Clin Microbiol Infect*. 2023;29(2):215-220.

doi: 10.1016/j.cmi.2022.09.001

45. Keech C, Albert G, Cho I, *et al.* Phase 1-2 Trial of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine. *N Engl J Med*. 2020;383(24):2320-2332.

doi: 10.1056/NEJMoa2026920

46. Heath PT, Galiza EP, Baxter DN, *et al.* Safety and Efficacy of the NVX-CoV2373 Coronavirus Disease 2019 Vaccine at Completion of the Placebo-Controlled Phase of a Randomized Controlled Trial. *Clin Infect Dis*. 2023;76(3):398-407.

doi: 10.1093/cid/ciac803

47. Parums DV. Editorial: First Approval of the Protein-Based Adjuvanted Nuvaxovid (NVX-CoV2373) Novavax Vaccine for SARS-CoV-2 Could Increase Vaccine Uptake and Provide Immune Protection from Viral Variants. *Med Sci Monit*. 2022;28:e936523.

doi: 10.12659/MSM.936523

48. Voysey M, Clemens SAC, Madhi SA, *et al.* Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: An interim analysis of four randomized controlled trials in Brazil, South Africa, and the UK. *Lancet*. 2021;397(10269):99-111.

doi: 10.1016/S0140-6736(20)32661-1

49. GOV.UK. Regulatory Approval of COVID-19 Vaccine AstraZeneca. 2021. Accessed April 23, 2026. https://www.gov.uk/government/publications/regulatory-approval-of-covid-19-vaccine-astrazeneca.

50. China Approves Two More Domestic COVID-19 Vaccines for Public Use. Accessed April 23, 2026. https://www.reuters.com/article/idUSKBN2AP1V8/

51. Balakrishnan VS. The arrival of Sputnik V. *Lancet Infect Dis*. 2020;20(10):1128.

doi: 10.1016/S1473-3099(20)30709-X

52. Logunov DY, Dolzhikova IV, Shcheblyakov DV, *et al.* Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: An interim analysis of a randomized controlled phase 3 trial in Russia. *Lancet*. 2021;397(10275):671-681.

doi: 10.1016/S0140-6736(21)00234-8

53. Callaway E. Russia's fast-track coronavirus vaccine draws outrage over safety. *Nature*. 2020;584(7821):334-335.

doi: 10.1038/d41586-020-02386-2

54. Sadoff J, Gray G, Vandebosch A, *et al.* Final Analysis of Efficacy and Safety of Single-Dose Ad26.COV2.S. *N Engl J Med*. 2022;386(9):847-860.

doi: 10.1056/NEJMoa2117608

55. Food and Drug Administration. *Fact Sheet for Healthcare Providers Administrating Vaccine (Vaccination Providers), Emergency Use Authorization (EUA) of the Janssen COVID-19 Vaccine to Prevent Coronavirus Disease (COVID-19).* Silver Spring, MD, USA: Food and Drug Administration; 2019. Accessed April 23, 2026. https://www.fda.gov/media/146304/download

56. Yao A, Jia S, Cheng X, *et al.* Immunogenicity and safety of a booster dose of the COVID-19 DNA vaccine in healthy adults aged 18 years and above: a single-center, randomized, observer-blind, placebo-controlled phase 2 trial. *BMC Infect Dis*. 2025;25(1):750.

doi: 10.1186/s12879-025-11140-w

57. Momin T, Kansagra K, Patel H, *et al.* Safety and Immunogenicity of a DNA SARS-CoV-2 vaccine (ZyCoV-D): Results of an open-label, non-randomized phase I part of phase I/II clinical study by intradermal route in healthy subjects in India. *eClinicalMedicine*. 2021;38:101020.

doi: 10.1016/j.eclinm.2021.101020

58. Khobragade A, Bhate S, Ramaiah V, *et al.* Efficacy, safety, and immunogenicity of the DNA SARS-CoV-2 vaccine (ZyCoV-D): The interim efficacy results of a phase 3, randomized, double-blind, placebo-controlled study in India. *Lancet*. 2022;399(10332):1313-1321.

doi: 10.1016/S0140-6736(22)00151-9

59. Mallapaty S. India's DNA COVID vaccine is a world first—More are coming. *Nature*. 2021;597(7875):161-162.

doi: 10.1038/d41586-021-02385-x

60. Sahin U, Muik A, Vogler I, *et al.* BNT162b2 vaccine induces neutralizing antibodies and poly-specific T cells in humans. *Nature*. 2021;595(7868):572-577.

doi: 10.1038/s41586-021-03653-6

61. Lamb YN. BNT162b2 mRNA COVID-19 Vaccine: First Approval. *Drugs*. 2021;81(4):495-501.

doi: 10.1007/s40265-021-01480-7

62. Baden LR, El Sahly HM, Essink B, *et al.* Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med*. 2021;384(5):403-416.

doi: 10.1056/NEJMoa2035389

63. U.S. Food and Drug Administration. FDA Takes Additional

Action in Fight against COVID-19 by Issuing Emergency Use Authorization for Second COVID-19 Vaccine. 2020. Accessed April 24, 2026. https://www.prnewswire.com/news-releases/fda-takes-additional-action-in-fight-against-covid-19-by-issuing-emergency-use-authorization-for-second-covid-19-vaccine-301196303.html

64. McKay PF, Hu K, Blakney AK, *et al.* Self-amplifying RNA SARS-CoV-2 lipid nanoparticle vaccine candidate induces high neutralizing antibody titers in mice. *Nat Commun*. 2020;11(1):3523.

doi: 10.1038/s41467-020-17409-9

65. Pollock KM, Cheeseman HM, Szubert AJ, *et al.* Safety and immunogenicity of a self-amplifying RNA vaccine against COVID-19: COVAC1, a phase I, dose-ranging trial. *eClinicalMedicine*. 2022;44:101262.

doi: 10.1016/j.eclinm.2021.101262

66. Szubert AJ, Pollock KM, Cheeseman HM, *et al.* COVAC1 phase 2a expanded safety and immunogenicity study of a self-amplifying RNA vaccine against SARS-CoV-2. *eClinicalMedicine*. 2023;56:101823.

doi: 10.1016/j.eclinm.2022.101823

67. Clinical Trials Registry-India. Safety, tolerability and immunogenicity of the candidate GEMCOVAC-19 (COVID-19) vaccine in healthy pediatric subjects of 5 to less than 18 years. Accessed April 14, 2026. https://gennova.bio/gemcovac-19-2/

68. HDT bio receives emergency use approval for covid-19 vaccine in India. Accessed April 20, 2026. https://www.pharmaceutical-technology.com/news/hdt-bio-vaccine-india-approval

69. Remuzzi G, Schiaffino S, Santoro MS, FitzGerald G, Melino G, Patrono C. Drugs for the prevention and treatment of COVID-19 and its complications: An update on what we learned in the past 2 years. *Front Pharmacol*. 2022;13:987816.

doi: 10.3389/fphar.2022.987816

70. Bugin K, Woodcock J. Trends in COVID-19 therapeutic clinical trials. *Nat Rev Drug Discov*. 2021;20(4):254-255.

doi: 10.1038/d41573-021-00037-3

71. Hromić-Jahjefendić A, Barh D, Uversky V, *et al.* Can COVID-19 Vaccines Induce Premature Non-Communicable Diseases: Where Are We Heading to? *Vaccines*. 2023;11(2):208.

doi: 10.3390/vaccines11020208

72. Anastasiou T, Sanidas E, Lytra T, Mimikos G, Gogas H, Mantzourani M. Update on Thromboembolic Event After Vaccination Against COVID-19. *Vaccines*. 2025;13(8):833.

doi: 10.3390/vaccines13080833

73. Heidecker B, Dagan N, Balicer R, *et al.* Myocarditis following COVID-19 vaccine: incidence, presentation, diagnosis, pathophysiology, therapy, and outcomes put into perspective. A clinical consensus document supported by the Heart Failure Association of the European Society of Cardiology (ESC) and the ESC Working Group on Myocardial and Pericardial Diseases. *Eur J Heart Fail*. 2022;24(11):2000-2018.

doi: 10.1002/ejhf.2669

74. Choi JYM, Smith DM. SARS-CoV-2 variants of concern. *Yonsei Med J*. 2021;62(11):961-968.

doi: 10.3349/ymj.2021.62.11.961

75. Gupta RK. Will SARS-CoV-2 variants of concern affect the promise of vaccines? *Nat Rev Immunol*. 2021;21(6):340-341.

doi: 10.1038/s41577-021-00556-5

76. Taucher C, Lazarus R, Dellago H, *et al.* Safety and immunogenicity against ancestral, Delta and Omicron virus variants following a booster dose of an inactivated whole-virus COVID-19 vaccine VLA2001: A randomized, controlled, phase 3COV-COMPARE trial. *J Infect*. 2023,87(3):242-254.

doi: 10.1016/j.jinf.2023.06.022

77. Chalkias S, Harper C, Vrbicky K, *et al.* A Bivalent Omicron-Containing Booster Vaccine against COVID-19. *N Engl J Med*. 2022;387(14):1279-1291.

doi: 10.1056/NEJMoa2208343

78. Wang Q, Guo Y, Bowen A, *et al.* XBB.1.5 monovalent mRNA vaccine booster elicits robust neutralizing antibodies against emerging SARS-CoV-2. *Cell Host Microbe*. 2024;32(3):315-321.e3.

doi: 10.1016/j.chom.2024.01.014

79. Li Y, Zhang X, Tai W, *et al.* A substitution at the cytoplasmic tail of the spike protein enhances SARS-CoV-2 infectivity and immunogenicity. *eBioMedicine*. 2024;110:105437.

doi: 10.1016/j.ebiom.2024.105437

80. Kiang MV, Bubar KM, Maldonado Y, Hotez PJ, Lo NC. Modeling Reemergence of Vaccine-Eliminated Infectious Disease Under Declining Vaccination in the US. *JAMA*. 2025;333(24):2176-2187.

doi: 10.1001/jama.2025.6495

81. Faizan A, Rehman T, Mughal S. Re-emergence of polio in Pakistan: Can the nation achieve the WPV1 eradication goal? *Health Sci Rep*. 2024;7(2):e1862.

doi: 10.1002/hsr2.1862

82. Wolff JA, Malone RW, Williams P, Chang W, Acsadi G, Jani A. Direct gene transfer into mouse muscle in vivo. *Science*. 1990;247(4949):1465-1468.

doi: 10.1126/science.1690918

83. World health Organization. COVID-19 vaccines. WHO COVID-19 dashboard. Accessed April 10, 2026. https://

data.who.int/dashboards/covid19/vaccines

84. Yasmin F, Najeeb H, Moeed A, *et al.* COVID-19 Vaccine Hesitancy in the United States: A Systematic Review. *Front Public Health*. 2021;9:770985.

    doi: 10.3389/fpubh.2021.770985

85. Wu J, Li Q, Silver Tarimo C, *et al.* COVID-19 Vaccine Hesitancy Among Chinese Population: A Large-Scale National Study. *Front Immunol*. 2021;12:781161.

    doi: 10.3389/fimmu.2021.781161

86. Willis DE, Presley J, Williams M, Zaller N, McElfish PA. COVID-19 vaccine hesitancy among youth. Hum. *Vaccin Immunother.* 2021;17(12):5013-5015.

    doi: 10.1080/21645515.2021.1989923

87. Biswas N, Mustapha T, Khubchandani J, Price JH. The Nature and Extent of COVID-19 Vaccination Hesitancy in Healthcare Workers. *J Community Health*. 2021;46(6):1244-1251.

    doi: 10.1007/s10900-021-00984-3

88. Ebrahimi OV, Johnson MS, Ebling S, *et al.* Risk, Trust, and Flawed Assumptions: Vaccine Hesitancy During the COVID-19 Pandemic. *Front Public Health*. 2021;9:700213.

    doi: 10.3389/fpubh.2021.700213

89. Storey D. COVID-19 Vaccine Hesitancy. *Global Health Sci. Pract*. 2022;10(1):e2200043.

    doi: 10.9745/GHSP-D-22-00043

90. Kricorian K, Civen R, Equils O. COVID-19 vaccine hesitancy: Misinformation and perceptions of vaccine safety. *Hum Vaccin Immunother*. 2022;18(1):1950504.

    doi: 10.1080/21645515.2021.1950504

91. Lunn PD, Timmons S. Public misperceptions of COVID-19 vaccine effectiveness and waning: experimental evidence from Ireland. *Public Health***.** 2023;214:81-84.

    doi: 10.1016/j.puhe.2022.11.002

92. Rosa SS, Prazeres DMF, Azevedo AM, Marques MPC. mRNA vaccines manufacturing: Challenges and bottlenecks. *Vaccine*. 2021;39(16):2190-2200.

    doi: 10.1016/j.vaccine.2021.03.038

93. Kis Z. Stability Modelling of mRNA Vaccine Quality Based on Temperature Monitoring throughout the Distribution Chain. *Pharmaceutics*. 2022;14(2):430.

    doi: 10.3390/pharmaceutics14020430

94. Kis Z, Kontoravdi C, Shattock R, Shah N. Resources, Production Scales and Time Required for Producing RNA Vaccines for the Global Pandemic Demand. *Vaccines*. 2020;9(1):3.

    doi: 10.3390/vaccines9010003

95. Walther J, Godawat R, Hwang C, Abe Y, Sinclair A, Konstantinov K. The business impact of an integrated continuous biomanufacturing platform for recombinant protein production. *J Biotechnol*. 2015;213:3-12.

    doi: 10.1016/j.jbiotec.2015.05.010

96. Kapoor Y, Meyer RF, Ferguson HM, *et al.* Flexibility in Drug Product Development: A Perspective. *Mol Pharm*. 2021;18(7):2455-2469.

    doi: 10.1021/acs.molpharmaceut.1c00210

97. Gruber P, Marques MPC, O'Sullivan B, Baganz F, Wohlgemuth R, Szita N. Conscious coupling: The challenges and opportunities of cascading enzymatic microreactors. *Biotechnol J*. 2017;12(7):1700030.

    doi: 10.1002/biot.201700030

98. Vogel AB, Lambert L, Kinnear E, *et al.* Self-amplifying RNA vaccines give equivalent protection against influenza to mRNA vaccines but at much lower doses. *Mol Ther*. 2018;26(2):446-455.

    doi: 10.1016/j.ymthe.2017.11.017

99. Halan V, Maity S, Bhambure R, Rathore AS. Multimodal Chromatography for Purification of Biotherapeutics - A Review. *Curr Protein Pept Sci*. 2018;20(1):4-13.

    doi: 10.2174/1389203718666171020103559

100. Alejo T, Toro-Cordova A, Fernandez L, *et al.* Comprehensive Optimization of a Freeze-Drying Process Achieving Enhanced Long-Term Stability and In Vivo Performance of Lyophilized mRNA-LNPs. *Int J Mol Sci*. 2024;25(19):10603.

    doi: 10.3390/ijms251910603

101. Das MK. COVID-19 vaccine and the cold chain implications for global adoption. *Indian J Public Health*. 2021;65(3):307-310.

    doi: 10.4103/ijph.IJPH_1353_20

102. Zhang N-N, Li X-F, Deng Y-Q, *et al.* Thermostable mRNA Vaccine against COVID-19. *Cell*. 2020;182(5):1271-1283. e16.

    doi: 10.1016/j.cell.2020.07.024

103. Coleman HJ, Rauch M, Langsfeld E, *et al.* Lipid-free, thermostable mRNA vaccines prepared using atomic layer deposition. *J Pharm Sci*. 2026;115(2):104066.

    doi: 10.1016/j.xphs.2025.104066

104. Nattrass N. Promoting conspiracy theory: From AIDS to COVID-19. *Glob Public Health*. 2023:18(1):2172199.

    doi: 10.1080/17441692.2023.2172199

105. Hammad AM, Al-Qerem W, Abu Zaid A, Khdair S, Hall FS. Misconceptions Related to COVID 19 Vaccines Among the Jordanian Population: Myth and Public Health. *Disaster Med Public Health Prep*. 2022;17:e207.

doi: 10.1017/dmp.2022.143

106. Rabdano SO, Ruzanova EA, Verytachikh AE, *et al.* N-protein vaccine is effective against COVID-19: Phase 3, randomized, double-blind, placebo-controlled clinical trial. *J Infect*. 2024;89(5):106288.

doi: 10.1016/j.jinf.2024.106288

107. Jennewein MF, Schulz MD, Beaver S, *et al.* Intranasal replicon SARS-CoV-2 vaccine produces protective respiratory and systemic immunity and prevents viral transmission. *Mol Ther*. 2025;33(7):3286-3306.

doi: 10.1016/j.ymthe.2025.04.007

108. World Health Organization. Weekly epidemiological update on COVID-19 - 4 January 2023. Accessed April 15, 2026. https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---4-january-2023

109. Davis IM. SARS-CoV: Lessons learned; opportunities missed for SARS-CoV-2. *Rev Med Virol*. 2021;31(1):1-6.

doi: 10.1002/rmv.2152