Vaccine Development Strategies for SARS-CoV-2

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# Authors

**COVID-19 Review Consortium:** Vikas Bansal, John P. Barton, Simina M. Boca, Joel D Boerckel, Christian Brueffer, James Brian Byrd, Stephen Capone, Shikta Das, Anna Ada Dattoli, John J. Dziak, Jeffrey M. Field, Soumita Ghosh, Anthony Gitter, Rishi Raj Goel, Casey S. Greene, Marouen Ben Guebila, Daniel S. Himmelstein, Fengling Hu, Nafisa M. Jadavji, Jeremy P. Kamil, Sergey Knyazev, Likhitha Kolla, Alexandra J. Lee, Ronan Lordan, Tiago Lubiana, Temitayo Lukan, Adam L. MacLean, David Mai, Serghei Mangul, David Manheim, Lucy D'Agostino McGowan, Jesse G. Meyer, Ariel I. Mundo, Amruta Naik, YoSon Park, Dimitri Perrin, Yanjun Qi, Diane N. Rafizadeh, Bharath Ramsundar, Halie M. Rando, Sandipan Ray, Michael P. Robson, Vincent Rubinetti, Elizabeth Sell, Lamonica Shinholster, Ashwin N. Skelly, Yuchen Sun, Yusha Sun, Gregory L Szeto, Ryan Velazquez, Jinhui Wang, Nils Wellhausen

Authors with similar contributions are ordered alphabetically.

## 0.1 Abstract

Vaccines have revolutionized the relationship between people and disease. In the 21st century, several emergent viruses have emphasized the particular value of rapid and scalable vaccine development programs. During the current pandemic caused by *Severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2), recent biotechnological advances in vaccine design have facilitated the development and deployment of vaccines at an unprecedented pace. The genome sequence of SARS-CoV-2 was released in January 2020, allowing for global efforts in vaccine development to begin within two weeks of the international community becoming aware of the new viral threat. Both established vaccine platforms and more recently developed technologies have been explored against SARS-CoV-2. Although historically a slow process, vaccine development in the face of COVID-19 accelerated so much that less than a year into the pandemic, some vaccine candidates had reported interim phase III clinical trial data and were being administered in countries around the world.

In this review, we contextualize COVID-19 vaccine development in the broader vaccine landscape. We describe where these candidates currently stand in terms of efficacy, safety, and approval and discuss patterns in worldwide distribution. Vaccines have nearly 500 years of history, but the SARS-CoV-2 pandemic provides an exceptional illustration of how rapidly vaccine development technology has advanced in the last two decades in particular.

## 0.2 Importance

The SARS-CoV-2 pandemic has caused untold damage globally, presenting unusual opportunities and demands in vaccine development. As of May 6, 2022, SARS-CoV-2 has infected over 516,758,993 and taken the lives of 6,249,626 people globally. The development, production, and distribution of vaccines is imperative to saving lives, preventing illness, and reducing the economic and social burdens caused by the COVID-19 pandemic. Effective deployment is critical to reducing the susceptibility of worldwide populations, especially in light of emerging variants. This review provides historical context for the current state of vaccine development and highlights the main strategies utilized for COVID-19 vaccine candidates, their clinical appraisal, and their distribution. These technologies have revolutionized the timescale at which countries can mount a response to an emerging viral threat and provide potential for mitigating future threats before their damage reaches the levels caused by SARS-CoV-2. As the SARS-CoV-2 virus has evolved, they also provide insight into how these technologies have to adapt on incredibly short timescales.

## 0.3 Introduction

The development of vaccines is widely considered one of the most important medical advances in human history. Over the past 150 years, several new approaches to vaccine development have emerged [[1](#ref-YY3x3bBV)]. Today, the requirements for developing and deploying a vaccine are complex and often require coordination between government, industry, academia, and philanthropic entities [[2](#ref-plfPrQP7)]. Flu-like illnesses caused by viruses that follow an annual pattern are a major target of vaccine development programs. However, vaccine development has historically been slow. The past 20 years have seen several previously unknown viruses emerge and rise rapidly to pose a global threat, challenging vaccine developers to explore approaches that would facilitate a rapid response to novel viruses.

Emergent viral threats of the 21st century include severe acute respiratory syndrome (SARS), “swine flu” (H1N1), Middle East respiratory syndrome (MERS), Ebola virus disease (EVD), Zika virus, and now COVID-19, all of which have underscored the importance of a rapid global response to a new infectious virus. Because vaccines fail to provide immediate prophylactic protection or treatment of ongoing infections, their application to most of these epidemics has been limited [[3](#ref-181QWa7HL)]. One of the more successful recent vaccine development programs was for H1N1 influenza. This program benefited from the strong existing infrastructure for influenza vaccines along with the fact that regulatory agencies had determined that vaccines produced using egg- and cell-based platforms could be licensed under the regulations used for a strain change [[4](#ref-HyYY2agc)]. Although a monovalent H1N1 vaccine was not available before the pandemic peaked in the United States and Europe, it became available soon afterward as a stand-alone vaccine that was eventually incorporated into commercially available seasonal influenza vaccines [[4](#ref-HyYY2agc)]. Critiques of the production and distribution of the H1N1 vaccine have stressed the need for alternative development-and-manufacturing platforms that can be readily adapted to new pathogens.

Vaccine technologies that require only minor adjustments for novel viral threats are appealing because this modular approach would mean they could enter trials quickly in response to a new pathogen of concern. Traditional vaccine technologies were built on the principle of using either a weakened version of the virus or a fragment of the virus, while recent years have seen a paradigm shift towards reverse vaccinology. Reverse vaccinology emphasizes a hypothesis-free approach to vaccine development [[5](#ref-jU9YFYvB)]. This strategy was explored during development of a DNA vaccine against the Zika virus [[6](#ref-u0dESADU)]. While once again the disease was controlled before the vaccine became available [[4](#ref-HyYY2agc)], the response demonstrated the potential for modular technologies to facilitate a response to emerging viral threats [[6](#ref-u0dESADU)]. The potential for such vaccines to benefit the field of oncology has encouraged vaccine developers to invest in next-generation approaches, which has spurred the diversification of vaccine development programs [[7](#ref-wPl93ATP),[8](#ref-BsrTDzJ2)]. As a result, during the COVID-19 pandemic, these modular technologies have taken center stage in controlling a viral threat for the first time.

The pandemic caused by SARS-CoV-2 has highlighted a confluence of circumstances that positioned vaccine development as a key player in efforts to control the virus and mitigate its damage. This virus did not follow the same trajectory as other emergent viruses of recent note, such as SARS-CoV-1, MERS-CoV, and Ebola virus, none of which reached the level of pandemic. Spread of the SARS-CoV-2 virus has remained out of control in many parts of the world into 2022, especially with the emergence of novel variants exhibiting increased rates of transmission [[9](#ref-GdZc4Yyd)]. While, for a variety of reasons, SARS-CoV-2 was not controlled as rapidly as the viruses underlying prior 21st century epidemics [[10](#ref-njpLhBui)], vaccine development technology had also progressed based on these and other prior viral threats to the point that a rapid international vaccine development response was possible.

Vaccines bolster the immune response to the virus at the population level, thereby driving a lower rate of disease and likely significantly reducing infection even for a highly infectious virus like SARS-CoV-2. The first critical step towards developing a vaccine against SARS-CoV-2 was characterizing the viral target, which happened extremely early in the COVID-19 outbreak with the sequencing and dissemination of the viral genome in early January 2020 [[11](#ref-vlGP3RAU)] (Figure [1](#fig:virus)). This genomic information allowed for an early identification of the sequence of the spike (S) protein (Figure [1](#fig:virus)), which is the antigen and induces an immune response [[12](#ref-Vnbw9o3T),[13](#ref-13wCBLnnu)].

The Coalition for Epidemic Preparedness Innovations (CEPI) is coordinating global health agencies and pharmaceutical companies to develop vaccines against SARS-CoV-2. As early as September 2020, there were over 180 vaccine candidates against SARS-CoV-2 in development [[14](#ref-dqpEe5Lz)]. While little is currently known about immunity to SARS-CoV-2, vaccine developers typically tests for serum neutralizing activity, as this has been designated a biomarker for adaptive immunity in other respiratory illnesses [[15](#ref-wiGjCZC8)]. However, unlike in efforts to develop vaccines for prior viral threats, the duration of the COVID-19 pandemic has made it possible to test vaccines in phase III trials where the effect of the vaccine on a cohort’s likelihood of contracting SARS-CoV-2 is evaluated. With vaccine candidates at all stages of development, including full approval of some vaccines, the vaccine development landscape for COVID-19 includes vaccines produced by a wide array of technologies. Examining the vaccine development programs tackling the COVID-19 pandemic alongside other 21st century efforts to control emerging viral threats demonstrates the significant biotechnological advances in this field and the importance of modular and adaptable approaches to vaccination. Here, we review the various technologies being explored for the development of SARS-CoV-2 vaccines globally.



Figure 1: **Structure of the SARS-CoV-2 virus.** The development of vaccines depends on the immune system recognizing the virus. Here, the structure of SARS-CoV-2 is represented both in the abstract and against a visualization of the virion. The abstracted visualization was made using BioRender [[16](#ref-14FBejgLM)] and the microscopy was conducted by the National Institute of Allergy and Infectious Diseases [[17](#ref-Jzj97hJh)].

## 0.4 Cross-Platform Considerations in Vaccine Development

Certain design decisions are relevant to vaccine development across multiple platforms. One applies to platforms that deliver the antigen, which in the case of SARS-CoV-2 vaccines is the Spike (S) protein. The prefusion conformation of the SARS-CoV-2 S protein, which is the structure before the virus fuses to the host cell membrane, is metastable [[18](#ref-R7Xdh5nH)], and the release of energy during membrane fusion drives this process forward following destabilization [[19](#ref-17DSmRo9H),[20](#ref-3uddYea8)]. Due to the significant conformational changes that occur during membrane fusion [[21](#ref-qcVbT0w4),[22](#ref-hIc3bKWe),[23](#ref-zK0rFpz1)], S protein immunogens that are stabilized in the prefusion conformation are of particular interest, especially because a prefusion stabilized MERS-CoV S antigen was found to elicit an improved antibody response [[24](#ref-oghHqZDt)]. Moreover, the prefusion conformation offers an opportunity to target S2, a region of the S protein that accumulates mutations at a slower rate [[24](#ref-oghHqZDt),[25](#ref-13wWdgODZ),[26](#ref-OVsxrEuX)] (see also [[9](#ref-GdZc4Yyd)]). Vaccine developers can stabilize the prefusion conformer by selecting versions of the S protein containing mutations that lock the position [[27](#ref-lvq9hGmj)]. The immune response to the spike protein when it is stabilized in this conformation is improved over other S structures [[28](#ref-10UC562ga)]. Thus, vaccines that use this prefusion stabilized conformation are expected to not only offer improved immunogenicity, but also be more resilient to the accumulation of mutations in SARS-CoV-2.

Another cross-platform consideration is the use of adjuvants. Adjuvants include a variety of molecules or larger microbial-related products that affect the immune system broadly or an immune response of interest. They can either be comprised of or contain immunostimulants or immunomodulators. Adjuvants are sometimes included within vaccines in order to enhance the immune response. Different adjuvants can regulate different types of immune responses, so the type or combination of adjuvants used in a vaccine will depend on both the type of vaccine and concern related to efficacy and safety. A variety of possible mechanisms for adjuvants have been investigated [[29](#ref-13bVbfc5h),[30](#ref-122h6fIxE),[31](#ref-uO0uqhxc)].

## 0.5 COVID-19 Vaccine Development Platforms



Figure 2: **Vaccine Development Strategies.** Several different strategies can and are being employed for the development of vaccines today. Each approach capitalizes on different features of the SARS-CoV-2 virus and delivery through a different platform. All of these approaches are being explored in the current pandemic.

The first administration of a dose of a COVID-19 vaccine to a human trial participant occurred on March 16, 2020 [[32](#ref-fQvzeptv),[33](#ref-1GA95MF2m)], marking an extremely rapid response to the emergence of SARS-CoV-2. Within a few weeks, at least 78 vaccine development programs were active [[33](#ref-1GA95MF2m)]. These programs employ a variety of technologies (Figure [2](#fig:vaccines)), ranging from established approaches to novel technologies that had never previously gone to market. As of May 6, 2022, 38 SARS-CoV-2 vaccines have been approved world wide and 27 are being administered throughout the world, with 12 billion doses administered across 223 countries. Many vaccines are available in only a subset of countries, and the types of vaccines available varies widely throughout the world. The status of individual vaccines continues to change and varies regionally.

### 0.5.1 Whole-Virus Vaccines

Whole-virus vaccines have the longest history among vaccine development approaches. Variolation, which is widely considered the first vaccination strategy in human history, is one example [[34](#ref-Q10m9bJ),[35](#ref-1Clt2Bek3)]. Famously employed against smallpox when healthy individuals were exposed to pus from an individual infected with what was believed to be either cowpox or horsepox [[34](#ref-Q10m9bJ),[35](#ref-1Clt2Bek3),[36](#ref-ZUHALvLg),[37](#ref-1DFnwhtrq)], variolation allowed healthy individuals to be infected with a mild case of a disease. While whole-virus vaccines can confer adaptive immunity, they also face safety concerns [[36](#ref-ZUHALvLg),[38](#ref-kC2tx3JC),[39](#ref-K0Ltu31S)]. As of 2005, most vaccines still used whole-virus platforms [[40](#ref-U9ZIZWkB)], and these technologies remain valuable tools in vaccine development today [[1](#ref-YY3x3bBV)]. Whole virus vaccine candidates have been developed for COVID-19 using both live attenuated viruses and inactivated whole viruses.

Table 1: Approved whole-virus vaccines [[41](#ref-jswAyWIs)]

| Vaccine | Company |
| --- | --- |
| Covaxin | Bharat Biotech |
| KoviVac | Chumakov Center |
| Turkovac | Health Institutes of Turkey |
| FAKHRAVAC (MIVAC) | Organization of Defensive Innovation and Research |
| QazVac | Research Institute for Biological Safety Problems (RIBSP) |
| KCONVAC | Shenzhen Kangtai Biological Products Co |
| COVIran Barekat | Shifa Pharmed Industrial Co |
| Covilo | Sinopharm (Beijing) |
| Inactivated (Vero Cells) | Sinopharm (Wuhan) |
| CoronaVac | Sinovac |
| VLA2001 | Valneva |

#### 0.5.1.1 Live-Attenuated Virus Vaccines

**Mechanism:** LAV, also known as replication-competent vaccines, use a weakened, living version of a disease-causing virus or a version of a virus that is modified to induce an immune response [[14](#ref-dqpEe5Lz)]. Whether variolation is the first example of a live-attenuated virus (LAV) being used to induce immunity is debated [[1](#ref-YY3x3bBV),[38](#ref-kC2tx3JC)], but subsequent efforts to incorporate attenuated viruses relied on either the identification of related viruses that were less virulent in humans (e.g., cowpox/horsepox or rotavirus vaccines) or culture of a virus *in vitro* [[1](#ref-YY3x3bBV),[36](#ref-ZUHALvLg)]. Today, a virus can be attenuated by passaging it in a foreign host until, due to selection pressure, the virus loses its efficacy in the original host. Alternatively, selective gene deletion or codon de-optimization can be utilized to attenuate the virus [[14](#ref-dqpEe5Lz)]. Foreign antigens can also be integrated into an attenuated viral vector [[42](#ref-4RuaSyLg)]. LAVs are also favored because they tend to be restricted to viral replication in the tissues around the location of inoculation [[43](#ref-iX8wXLPW)], and some can be administered intranasally [[14](#ref-dqpEe5Lz)].

**Prior Applications:** The first deliberate (albeit pathogen-naïve) attempt to develop an attenuated viral vaccine dates back to Louis Pasteur in 1885. The next intentional LAVs were developed against the yellow fever virus in 1935 and influenza in 1936 [[43](#ref-iX8wXLPW)]. Today, LAVs are used globally to prevent diseases caused by viruses such as measles, rubella, polio, influenza, varicella zoster, and the yellow fever virus [[44](#ref-wZ2tXSUH)]. There were attempts to develop LAVs against both SARS-CoV-1 and MERS-CoV [[45](#ref-7RHpaAHu)], but no vaccines were approved.

**Application to COVID-19:** LAVs have not been widely utilized against SARS-CoV-2 and COVID-19. All the same, there are at least five COVID-19 LAV candidates in the early (preclinical/phase I) stages of investigation. These candidates utilize different approaches. In one case, the vaccine delivers a noncleavable SARS-CoV-2 antigen prefusion conformation using a live-attenuated yellow fever virus [[42](#ref-4RuaSyLg)]. Several other candidates use codon-deoptimized SARS-CoV-2 [[46](#ref-nwyfEEPl),[47](#ref-iCUWeMfX),[48](#ref-xMxJTYge)], leveraging the fact that different organisms display different biases in which synonymous codons are preferred to select codons that will be less optimal in the target organism without altering the amino acids encoded [[49](#ref-P329FxPV)]. Another is a chimeric vaccine that integrates genomic content from multiple viruses to create a more stable LAV [[50](#ref-14GSJSuHC)]. A final LAV being evaluated against COVID-19 was not specifically developed against SARS-CoV-2; instead, Bacillus Calmette-Guerin (BCG) vaccines were being investigated for the prophylaxis of COVID-19 [[51](#ref-1CJtdlM6d)] because they are known to exert protective non-specific effects against other respiratory tract infections in in vitro and in vivo studies [[52](#ref-16FOT89K5)]. However, a multicenter trial that randomly assigned participants 60 years and older to vaccination with BCG (n = 1008) or placebo (n = 1006) after 12 months of follow-up found that BCG vaccination had no effect on the incidence of SARS-CoV-2 or other respiratory infections [[53](#ref-eHrzWQ6D)]. Despite these negative findings, BCG vaccination did induce a stronger antibody and cytokine response following COVID-19 infection.

**Safety and Efficacy:** Data is not yet available for human studies. In general, though safety associated with the production of LAVs was a major concern in the past, today manufacturers use safe and reliable methods to produce large quantities of vaccines once they have undergone rigorous preclinical studies and clinical trials to evaluate their safety and efficacy. However, one reason underlying the relatively slow emergence of LAV candidates against COVID-19 may be the risk presented to individuals who are immunocompromised [[54](#ref-bgKUtUIL)], which is an even greater concern when dealing with a novel virus and disease. Additionally, it is generally recognized that LAVs induce an immune response similar to natural infection, and they are favored because they induce long-lasting and robust immunity that can protect from disease. This strong protective effect is induced in part by the immune response to the range of viral antigens available from LAV, which tend to be more immunogenic than those from non-replicating vaccines [[38](#ref-kC2tx3JC),[45](#ref-7RHpaAHu),[55](#ref-zLL2yOJK)]. Additional data are needed to ascertain how this technology performs in the case of SARS-CoV-2.

#### 0.5.1.2 Inactivated Whole-Virus Vaccines

**Mechanism:** Inactivated whole-virus (IWV) vaccines are another well-established technology. These types of vaccines use full virus particles generally produced via cell culture that have been rendered non-infectious by chemical (i.e., formaldehyde or β-propiolactone [[56](#ref-PwjPrwXa)]) or physical (i.e., heat or ultraviolet radiation) means. In general, these vaccines mimic the key properties of the virus that stimulate a robust immune response, but the risk of adverse reactions is reduced because the virus is inactivated and thus unable to replicate. Though these viral particles are inactivated, they retain the capacity to prime the immune system. The size of the virus particle makes it ideal for uptake by an antigen-presenting cell (APC), which leads to the stimulation of helper T-cells [[57](#ref-7Knbo28h)]. Additionally, the array of epitopes on the surface of the virus increases antibody binding efficiency [[57](#ref-7Knbo28h)]. The native conformation of the surface proteins, which is also important for eliciting an immune response, is preserved using these techniques [[58](#ref-10peSXMZx)]. Membrane proteins, which support B-cell responses to surface proteins, are also induced by this method [[59](#ref-iAa7uWOm)].

**Prior Applications:** IWV vaccines have been a valuable tool in efforts to control many viruses. Some targets of IWV vaccines have included influenza viruses, poliovirus, and hepatitis A virus. Inactivated vaccines are generally considered the fastest to generate once the pathogenic virus has been isolated and can be passaged in cell culture [[45](#ref-7RHpaAHu)], although this has not been the case for the COVID-19 pandemic. Past applications to HCoV have focused predominantly on SARS-CoV-1.

Preclinical studies have demonstrated that IWV SARS-CoV-1 vaccine candidates elicited immune responses *in vivo*. These vaccines generated neutralizing antibody titers at concentrations similar to those evoked by recombinant protein vaccines [[58](#ref-10peSXMZx),[60](#ref-1DymXCWa0)]. Studies in ferrets and non-human primates demonstrated that IWV vaccines can offer protection against infection due to neutralizing antibody and SARS-CoV-1-specific T cell responses [[61](#ref-4Hh1wpwV)].

However, several attempts to develop IWV vaccines against both SARS-CoV-1 and MERS-CoV were hindered by incidences of vaccine-associated disease enhancement (VADE) in preclinical studies [[62](#ref-4AwyoMvQ)]. In one example of a study in macaques, an inactivated SARS-CoV-1 vaccine induced even more severe lung damage than the virus due to an enhanced immune reaction [[63](#ref-ZXAfLbxM)]. Independent studies in mice also demonstrated evidence of lung immunopathology due to VADE in response to MERS-CoV IWV vaccination [[64](#ref-ihrfEtMq),[65](#ref-8qw9OBKX)]. The exact mechanisms responsible for VADE remain elusive due to the specificity of the virus-host interactions involved, but VADE is the subject of investigation in preclinical SARS-CoV-2 vaccine studies to ensure the safety of any potential vaccines that may reach phase I trials and beyond [[62](#ref-4AwyoMvQ)].

**Application to COVID-19:** Several whole-virus vaccines have been developed against COVID-19 and are available in countries around the world. As of May 6, 2022, 11 vaccines developed with IWV technology are being distributed in 114 countries (Figure [3](#fig:iwv-distrib)). One, CoronaVac, was developed by Beijing-based biopharmaceutical company Sinovac. They inactivated a SARS-CoV-2 strain collected in China with β-propiolactone and propagated it using Vero cells [[45](#ref-7RHpaAHu)]. The vaccine is coupled with an aluminum adjuvant [[45](#ref-7RHpaAHu)]. In phase I and II clinical trials, CoronaVac elicited a strong immunogenic response in animal models and the development of neutralizing antibodies in human participants [[66](#ref-Ozya5HP5),[67](#ref-14fILrRWg),[68](#ref-N1txjPtt)]. Administration followed a prime-boost regimen using a 0.5 ml dose containing 3 μg of inactivated SARS-CoV-2 virus per dose [[69](#ref-1A5wiKQAW)]. Results from a two-dose phase III trial following a 14-day prime boost became available in late 2020 [[70](#ref-1FF7JOwSH)], and an interim analysis identified specific IgG neutralizing antibodies against S1-RBD and a robust IFN-γ secreting T cell response was induced via immunization with CoronaVac [[71](#ref-UERG6dAd)]. CoronaVac was approved for use in China and has been granted emergency use in XX countries, including Brazil, Cambodia, Chile, Colombia, Laos, Malaysia, Mexico, Turkey, Ukraine, and Uruguay [82]. In August 2021, Sinovac reported that they had produced over a billion doses of CoronaVac [[72](#ref-wByD9WaX)].

Similarly, two inactivated vaccine candidates were developed following a similar approach by the stated-owned China National Pharmaceutical Group Co., Ltd., more commonly known as Sinopharm CNBG. Their BBIBP-CorV vaccine was developed in Beijing using the HB02 strain of SARS-CoV-2. At their Wuhan Institute, they developed a second vaccine using the WIV04 strain of SARS-CoV-2 [[73](#ref-miMRIMwa)]. The viruses were purified, propagated using Vero cells, isolated, and inactivated using β-propiolactone [[73](#ref-miMRIMwa),[74](#ref-VlnLw2HV)]. These vaccines are adjuvanted with aluminum hydroxide [[73](#ref-miMRIMwa),[74](#ref-VlnLw2HV)]. Preclinical studies indicated that the BBIBP-CorV vaccine induced sufficient neutralizing antibody titers in mice, and a prime-boost immunization scheme of 2 μg/dose was sufficient to protect rhesus macaques from disease [[74](#ref-VlnLw2HV)]. For the other vaccine, neutralizing antibodies were detected in all groups 14 days after the final dose in the phase I part of the trial [[75](#ref-T3MYavsH)], with similar findings reported in interim phase II data [[75](#ref-T3MYavsH)].

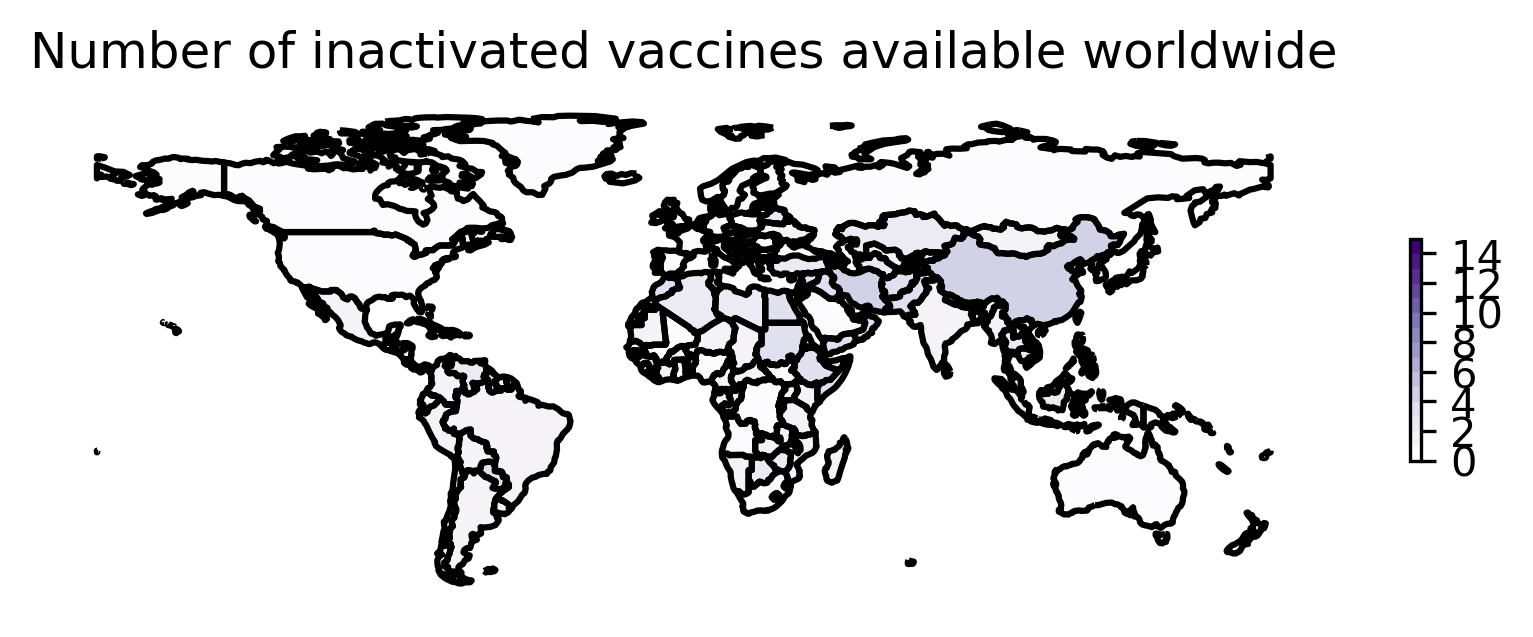


Figure 3: **Worldwide availability of vaccines developed using inactivated whole viruses.** This figure reflects the number of vaccines based on whole inactivated virus technology that were available in each country as of May 6, 2022. These data are retrieved from Our World in Data <!-To Do: Cite–> and plotted using geopandas. See https://greenelab.github.io/covid19-review/ for the most recent version of this figure, which is updated daily.

Other programs have been led through industry partnerships with governmental organizations. Another IWV vaccine comes from India, where Bharat Biotech International Ltd., which is the biggest producer of vaccines globally, Bharat Biotech International Ltd., collaborated with the Indian Council of Medical Research (ICMR) - National Institute of Virology (NIV) to develop COVAXIN®, also referred to as BBV152. Preclinical studies of COVAXIN® in hamsters [[76](#ref-bcGxW9fA)] and macaques [[77](#ref-GgdjKrYi)] indicated that the vaccine induced protective responses deemed sufficient to move forward to human trials. Phase I and phase I/II studies indicated that COVAXIN® adjuvanted with alum and a Toll-like receptor 7/8 (TLR7/8) agonist was safe and immunogenic and that it induced Th1-skewed memory T-cell responses [[78](#ref-CGuGeB7m),[79](#ref-GxQSMH5l)]. As of September 2021, COVAXIN® has been approved for emergency use in Guyana, India, Iran, Zimbabwe, and Nepal, Mauritius, Mexico, Nepal, Paraguay, and the Philippines [[80](#ref-19tYVbg8H)].

**Trial Safety and Efficacy:** In general, IWV vaccine candidates have been well-tolerated in clinical trials. Safety analysis of the CoronaVac vaccine during the phase II trial revealed that most adverse reactions were either mild (grade 1) or moderate (grade 2) in severity. In adults aged 18 to 59 years receiving a variety of dosage schedules, site injection pain was consistently the most common symptom reported [[68](#ref-N1txjPtt)]. In older adults, the most common local and systemic reactions were pain at the injection site (9%) and fever (3%), respectively [[66](#ref-Ozya5HP5)]. In phase III trials, minimal side effects were reported [[70](#ref-1FF7JOwSH)]. For COVAXIN, only mild to moderate side-effects reported upon immunization [[78](#ref-CGuGeB7m),[79](#ref-GxQSMH5l)], and in phase II trials, the BBIBP-CorV vaccine appeared well-tolerated, with 23% of participants in the vaccine condition (482 total participants, 3:1, vaccine:placebo) reporting at least one adverse reaction characterized as mild to moderate [[81](#ref-fPGgVKYL)]. However, both CoronaVac and SinoPharm’s WIV04 vaccine trials were affected by concerns about adverse events. In CoronaVac’s trial of adults 18-59, 2% (n=7) of participants reported severe adverse events [[66](#ref-Ozya5HP5)], causing the trial to be halted for investigation [[82](#ref-aq22z8M7)]. They were determined to be unrelated to the vaccine [[66](#ref-Ozya5HP5)]; [[82](#ref-aq22z8M7)]], which is now widely distributed. Similarly, a trial of the SinoPharm WIV04 vaccine in Peru was briefly paused due to safety concerns in relation to neurological symptoms [[83](#ref-d09adg1G)], but this was later deemed unrelated to the vaccine, and the trial continued [[84](#ref-nxEJTLGU)].

In terms of efficacy, estimates of IWV vaccine efficacy during phase III trials varied widely, and in some cases, even estimates for a single vaccine candidate differed across analyses. In phase III trials, Sinopharm CNBG’s BBIBP-CorV vaccine made from the WIV04 strain achieved an efficacy of 72.8% and was well tolerated [[85](#ref-yN5KOfvE)]. In July 2021, COVAXIN’s overall vaccine efficacy was estimated at 77.8% for the prevention of COVID-19 based on a final enrollment of 25,798 people (~1:1 vaccine:placebo) [[86](#ref-n7BupOQ6)]. Sinopharm affiliates in the UAE in early December 2020 claimed the vaccine had 86% efficacy, which was later at odds with a Sinopharm Beijing affiliate that stated that the BBIBP-CorV vaccine had a 79.34% efficacy later that same month [[87](#ref-w7gO6yGn)]. CoronaVac demonstrated an efficacy of a little over 50% in Brazil, which was contested by Turkish officials claiming an efficacy of 91.25%, but ultimately after multiple announcements, the efficacy debate was settled at over 50% [[88](#ref-18mREgqUz),[89](#ref-V7MXd4X4)]. Subsequently, an interim analysis of the phase III randomized placebo-controlled trials conducted in Turkey enrolling 10,214 participants (~2:1 vaccine:placebo) indicated efficacy of 83.5%, with minimal side effects reported [[70](#ref-1FF7JOwSH)], and a prospective national cohort study in Chile reported an adjusted estimated effectiveness of 66% for the prevention of COVID-19 with an estimated 90% and 87% prevention of hospitalization and death, respectively [[90](#ref-q2wQJULu)]. Therefore, it is difficult to ascribe a particular efficacy to these vaccines given the variation in reports.

**Real-World Safety and Efficacy:** One of the major limitations of IWV vaccines is their susceptibility to losing efficacy due to mutations in the epitopes of the circulating virus [[39](#ref-K0Ltu31S)]. This loss of specificity over time is likely to be influenced by the evolution of the virus, and specifically by the rate of evolution in the region of the genome that codes for the antigen. The beta variant appears to be more resistant to neutralizing antibodies in sera from individuals immunized with Sinovac than the alpha variant or wildtype virus, indicating that emerging variants may be of concern [[91](#ref-s2O5iyCV)]. In agreement with previous studies demonstrating sera from individuals vaccinated with COVAXIN® efficiently neutralized the alpha variant (B.1.1.7) and the delta variant (B.1.617.2) [[92](#ref-lr7INjf6),[93](#ref-UYE3NvU4),[94](#ref-IvOEe7bV)], the phase III trial reported a 65.2% efficacy against the delta variant (B.1.617.2) [[86](#ref-n7BupOQ6)]. However, studies suggested the beta variant was more resistant (compared to the wildtype and alpha variants) to neutralizing antibodies in sera from individuals immunized with Sinovac [[91](#ref-s2O5iyCV)].  
Indeed, another preprint determined that sera from individuals immunized with COVAXIN® had effective neutralizing antibodies against the delta variant and the so-called delta plus variant (AY.1) [[92](#ref-lr7INjf6)]. Notably, a preprint reported that antisera from 12 people immunized with BBIBP-CorV exhibited neutralizing antibody capacity against the beta variant (B.1.351), wild type SARS-CoV-2 (NB02), and one of the original variants of SARS-CoV-2 (D614G) [[95](#ref-w9KwrmQT)]. Another preprint including sera from 282 participants used a surrogate neutralizing assay, a test that generally correlates with neutralizing antibodies, to determine that BBIBP-CorV appears to induce neutralizing antibodies against the binding of the RBD of wild type SARS-CoV-2 and the alpha, beta, and delta variants to ACE2 [[96](#ref-GZ5Sf8Yd)]. Indeed, a study in *The New England Journal of Medicine* showed that the alpha variant exhibited very little resistance to neutralization by sera of those immunized with BBIBP-CorV, but the beta variant was more resistant to neutralization by almost a factor of 3 [[91](#ref-s2O5iyCV)]. The authors noted that no evidence of VADE was detected using this vaccine in phase II data [[75](#ref-T3MYavsH)].

However, concern was raised about the efficacy of CoronaVac following reports that over 350 doctors became ill with COVID-19 in Indonesia despite being immunized with CoronaVac [[97](#ref-fs7G9HyV)]. In addition to concerns raised by the evolution of SARS-CoV-2, it is important to consider the duration of immunity over time. Studies are underway to determine whether a booster immunization is required for several IWV vaccines, including CoronaVac [[98](#ref-1GcPxd9Bn)] and COVAXIN [[99](#ref-s1TGwKbT)]. A phase I/II clinical trial of CoronaVac in an elderly cohort (adults 60 years and older) in China determined that by 6 to 8 months following the second dose, neutralizing antibody titers were detected below the seropositive cutoff [[100](#ref-AcxNwvVQ)]. One preprint has reported that 6 months after the second vaccination, a booster dose of CoronaVac markedly increased geometric mean titers of SARS-CoV-2 neutralizing antibodies [[101](#ref-1BPnaMPs4)]. However, the reduction of neutralizing antibodies was ameliorated by a booster dose administered 8 months after the second CoronaVac dose.

A preprint study of healthcare workers in China has since indicated that a booster shot of BBIBP-CorV elevates B cell and T cell responses and increases neutralizing antibody titers [[102](#ref-QHtyW0Jz)]. In May 2021, the UAE announced it would consider booster shots for all citizens who had been immunized with BBIBP-CorV, which was shortly followed by a similar announcement in Bahrain, and by August 29th, 2021, the UAE mandated booster shots for all residents who had received BBIBP-CorV [[72](#ref-wByD9WaX)]. Additionally, heterogeneous vaccine boosters are also being considered in many cases. Chinese [[103](#ref-9oJ3sbrk)] and Chilean [[104](#ref-rCqhSryT)] researchers have opted to investigate options to administer different vaccines (e.g., an mRNA vaccine dose) as a booster dose to individuals who have already received two doses of CoronaVac. Another study has already determined that using the CanSino vaccine (Convidecia) instead of CoronaVac in a prime-boost vaccination regimen can induce a more robust immune response [[105](#ref-1HVWY0Qmv)]. Today, booster immunization is suggested for several whole-virus vaccines.

### 0.5.2 Subunit Vaccines

Table 2: Approved subunit vaccines [[41](#ref-jswAyWIs)]

| Vaccine | Company | Platform |
| --- | --- | --- |
| Zifivax | Anhui Zhifei Longcom | protein subunit |
| Noora vaccine | Bagheiat-allah University of Medical Sciences | protein subunit |
| Corbevax | Biological E Limited | protein subunit |
| Abdala | Center for Genetic Engineering and Biotechnology (CIGB) | protein subunit |
| Soberana 02 | Instituto Finlay de Vacunas Cuba | protein subunit |
| Soberana Plus | Instituto Finlay de Vacunas Cuba | protein subunit |
| Covifenz | Medicago | VLP |
| MVC-COV1901 | Medigen | protein subunit |
| Recombinant SARS-CoV-2 Vaccine (CHO Cell) | National Vaccine and Serum Institute | protein subunit |
| Nuvaxovid | Novavax | protein subunit |
| Razi Cov Pars | Razi Vaccine and Serum Research Institute | protein subunit |
| COVOVAX (Novavax formulation) | Serum Institute of India | protein subunit |
| TAK-019 (Novavax formulation) | Takeda | protein subunit |
| SpikoGen | Vaxine/CinnaGen Co. | protein subunit |
| Aurora-CoV | Vector State Research Center of Virology and Biotechnology | protein subunit |
| EpiVacCorona | Vector State Research Center of Virology and Biotechnology | protein subunit |

Efforts to overcome the limitations of live-virus vaccines led to the development of approaches first to inactivate viruses (circa 1900), leading to IWV vaccines, and then to purify proteins from viruses cultured in eggs (circa 1920) [[1](#ref-YY3x3bBV),[106](#ref-dggZoRQD)]. The purification of proteins led to the emergence of subunit vaccines. Today, such approaches may use antigens isolated from the surface of the viral particle that are key targets of the immune system (protein subunit vaccines), but advances in biological engineering have also facilitated the development of approaches like viral-like particle (VLP) vaccines using nanotechnology [[107](#ref-99C1xJ2E)].

**Mechanism:** Unlike whole-virus vaccines, which introduce the whole virus, subunit vaccines stimulate the immune system by introducing one or more proteins or peptides of the virus that have been isolated. The main advantage of this platform is that subunit vaccines are considered very safe, as the antigen alone cannot cause an infection [[108](#ref-1FfwyYaj7)]. Both protein subunit and VLP vaccines thus mimic the principle of whole virus vaccines but lack the genetic material required for replication, removing the risk of infection [[109](#ref-1Bxg7Wj6w)]. Protein subunit vaccines can stimulate antibodies and CD4+ T-cell responses [[110](#ref-12eGVhH5I),[111](#ref-lH2HMMZi)]. This platform is also favored for its consistency in production and defined components designed for a highly targeted immune response to a specific pathogen using synthetic immunogenic particles that can be designed to avoid allergen and reactogenic sequences [[112](#ref-124bnGvPp)]. The immune response generated by protein subunit vaccines is weaker, and adjuvants are usually required to boost the response [[113](#ref-mv42t1HV)] (see Appendix). These adjuvants are immunogenic substances, which include, for example, alum (aluminum hydroxide), squalene- or saponin-based adjuvants, and Freund’s incomplete/complete adjuvants [[112](#ref-124bnGvPp),[114](#ref-rioTBsLc)].

**Prior Applications:** Prior protein subunit vaccine development efforts for both SARS-CoV-1 and MERS-CoV have mostly focused on the immunogenic RBD of the S protein [[115](#ref-cLAQnckq),[116](#ref-1EirBATaN),[117](#ref-1AOG59epD)]. There have been several approaches investigated in the search for a potential SARS-CoV-1 vaccine, including vaccines targeting the full-length or trimeric S protein [[118](#ref-Ow2ICHez),[119](#ref-tzZeWNPV)], those focused on the RBD protein only [[115](#ref-cLAQnckq),[116](#ref-1EirBATaN),[117](#ref-1AOG59epD),[120](#ref-DsfTQFmb)] or non-RBD S protein fragments [[119](#ref-tzZeWNPV),[121](#ref-IYjNaaqv)], as well as the N and M proteins [[122](#ref-HvO79P9u),[123](#ref-VUcwpJKL),[124](#ref-7hbgOaiE)]; these efforts have been thoroughly reviewed elsewhere [[125](#ref-9Zv0eLa9)]. There have been examples of success in preclinical research including candidate RBD219N-1, a 218-amino-acid residue of the SARS-CoV-1 RBD that, when adjuvanted to aluminum hydroxide, was capable of eliciting a high RBD-specific and neutralizing antibody response in both pseudovirus and live virus infections of immunized mice [[126](#ref-8723Jsa)]. Several subunit-based approaches have also been used to investigate potential vaccines against MERS. Other strategies investigating the potential use of the full length S DNA have also been investigated in mice and rhesus macaques, which elicited immune responses [[127](#ref-GurQD2dO)], but these responses were not as effective as the combination of S DNA and the S1 subunit protein together [[127](#ref-GurQD2dO),[128](#ref-T7W7hnB9)]. Similarly to the SARS-CoV-1 vaccine candidates, the MERS-CoV protein subunit vaccine candidates generally target the RBD [[116](#ref-1EirBATaN),[125](#ref-9Zv0eLa9),[129](#ref-Mki0DaYb),[130](#ref-aApaHV1w),[131](#ref-deUFGhNI),[132](#ref-sfM5QV3m)], with some targeting the full length S protein [[24](#ref-oghHqZDt)], non-RBD protein fragments such as the SP3 peptide [[133](#ref-11Zz9H0Dl)], and the recombinant N-terminal domain (rNTD) [[134](#ref-ZXsnsfvb)]. No protein subunit vaccine for MERS-CoV has progressed beyond preclinical research to date. VLPs have been investigated for development of vaccines against MERS and SARS [[135](#ref-oqty7gXw),[136](#ref-eHe78HXD)] including testing in animal models [[137](#ref-cnYnzav2),[138](#ref-G87TcArN)], but once again, only preclinical data against HCoV has been collected [[139](#ref-jLJEygoA)]. However, protein subunit vaccines do play a role in public health and have contributed to vaccination against hepatitis B [[140](#ref-155fGivMy)] and pertussis [[141](#ref-CQog2bB7),[142](#ref-1CYqHUt3n)] since the 1980s and will likely continue to contribute to public health for the foreseeable future due to ongoing research in vaccines against influenza, SARS-CoV-2, Epstein-Barr virus, dengue virus, and human papillomavirus among others [[143](#ref-1FQlt5Lqz),[144](#ref-8dSIiLCt),[145](#ref-aAYBP21H)].

**Application to COVID-19:** The development of protein subunit vaccines against SARS-CoV-2 is a remarkable achievement given the short period of time since the emergence of SARS-CoV-2 in 2019, particularly considering these types of vaccines have not played a major role in previous pandemics. More than 20 protein subunit vaccines from companies such as Sanofi/GlaxoSmithKline, Nanogen, and the Serum Institute of India have entered clinical trials for COVID-19 since the beginning of the pandemic [[144](#ref-8dSIiLCt)] and 15 are being administered worldwide [[146](#ref-cWMPXfju)]. VLP vaccines have not progressed as rapidly, with only 1 VLP vaccines approved [[144](#ref-8dSIiLCt)] as of May 6, 2022. Most of these vaccines are designed using either the full-length S protein or the RBD of the S protein specifically as an antigen, although some use several different SARS-CoV-2 proteins [[108](#ref-1FfwyYaj7)]. As of March 30, 2022, 14 protein subunit vaccines are being distributed in 21 countries (Figure 4).

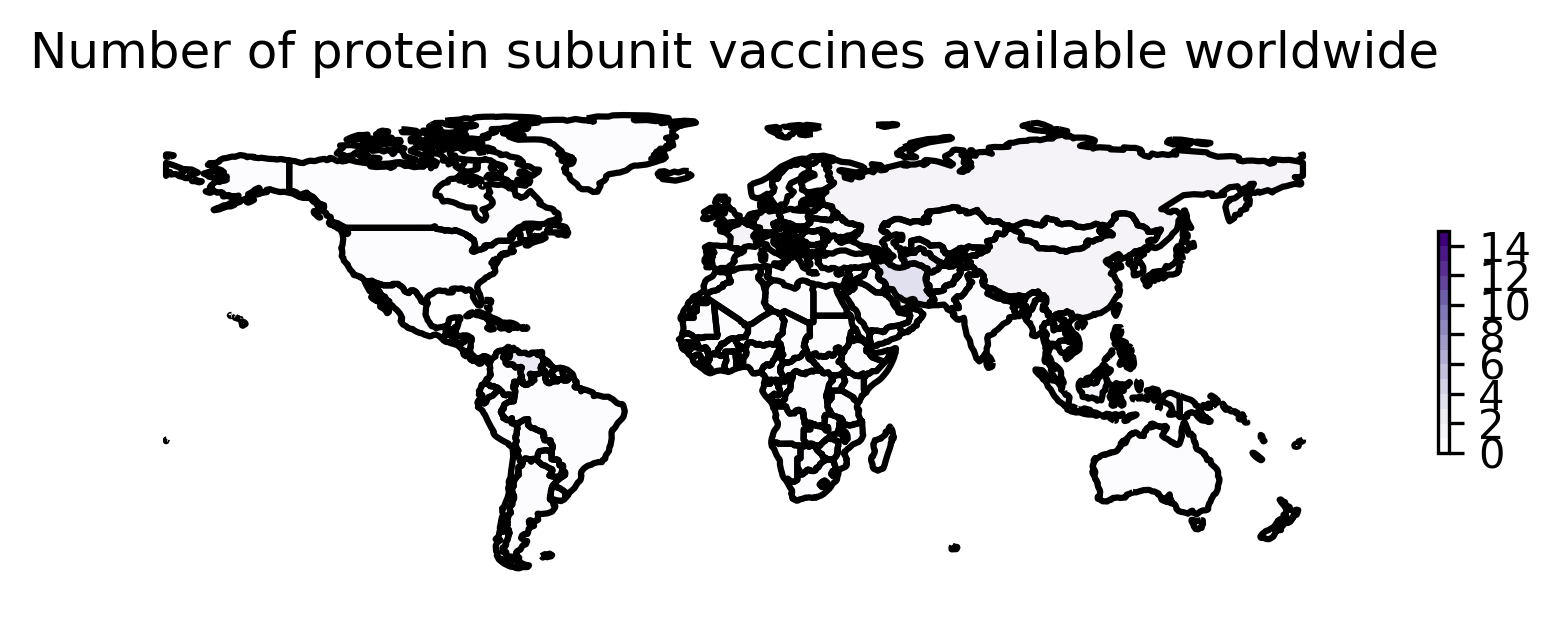


Figure 4: **Worldwide availability of vaccines developed using protein subunit.** This figure reflects the number of vaccines based on protein subunit technology that were available in each country as of May 6, 2022. These data are retrieved from Our World in Data <!-To Do: Cite–> and plotted using geopandas. See https://greenelab.github.io/covid19-review/ for the most recent version of this figure, which is updated daily.

One of the most prominent protein subunit vaccines against SARS-CoV-2 thus far is NVX-CoV2373 or Nuvaxovid, which is produced by U.S. company Novavax and partners. NVX-CoV2373 is a protein nanoparticle vaccine constructed from a mutated prefusion SARS-CoV-2 spike protein in combination with a specialized saponin-based adjuvant to elicit an immune response against SARS-CoV-2. The spike protein is recombinantly expressed in Sf9 insect cells [[147](#ref-Qk33ZrIC)], which have previously been used for several other FDA-approved protein therapeutics [[148](#ref-RQR2sOmx)], and contains mutations in the furin cleavage site (682-RRAR-685 to 682-QQAQ-685) along with two proline substitutions (K986P and V987P) that improve thermostability [[147](#ref-Qk33ZrIC)]. In preclinical mouse models, Novavax-CoV2373 elicited high anti-spike IgG titers 21 to 28 days post-vaccination that could neutralize the SARS-CoV-2 virus and protect the animals against viral challenge, with particularly strong effects when administered with the proprietary adjuvant Matrix-MTM [[147](#ref-Qk33ZrIC)]. In a phase I/II trial, a two-dose regimen of NVX-CoV2373 was found to induce anti-spike IgG levels and neutralizing antibody-titers exceeding those observed in convalescent plasma donated by symptomatic patients [[149](#ref-dMLXxGAI)]. In line with the preclinical studies, the use of Matrix-M adjuvant further increased anti-spike immunoglobulin levels and induced a Th1 response. In a phase III randomized, observer-blinded, placebo-controlled clinical trial in 14,039 participants, two 5-μg doses of NVX-CoV2373 or placebo were administered 21 days apart in a 1:1 ratio from late September to late November 2020 [[150](#ref-1D0f8OrG8)]. Novavax has since been approved in several places, including the United Kingdom [[151](#ref-q3wIcP4d)] and the E.U. [[152](#ref-P3YhxRob)] and applied for an EUA from the FDA in early 2022 [[153](#ref-6mHA0NU9)].

The leading example of a VLP approach applied to COVID-19 comes from Covifenz, a VLP vaccine developed by Canadian company Medicago [[154](#ref-pxEbK2Vl)]. This vaccine was developed using plant-based VLP technology [[155](#ref-18Xmc8WMR)] that the company had been investigating in order to develop a high-throughput quadrivalent VLP platform to provide protection against influenza [[156](#ref-WqqE64cZ)]. The approach utilizes *Nicotiana benthamiana*, an Australian relative of the tobacco plant, as an upstream bioreactor [[156](#ref-WqqE64cZ),[157](#ref-18mcJS5j4),[157](#ref-18mcJS5j4)]. Specifically, the *S* gene from SARS-CoV-2 in its prefusion conformation is inserted into a bacterial vector (*Agrobacterium tumefaciens*) that then infects the plant cells [[156](#ref-WqqE64cZ),[157](#ref-18mcJS5j4)]. Expression of the S glycoprotein causes the production of VLPs composed of S trimers anchored in a lipid envelope that accumulate between the plasma membrane and the cell wall of the plant cell [[157](#ref-18mcJS5j4)]. Because these VLPs do not contain the SARS-CoV-2 genome, they offer similar advantages to while mitigating the risks of whole-virus vaccines [[156](#ref-WqqE64cZ),[157](#ref-18mcJS5j4)].

In the Phase I study, Covifenz was administered to 180 Canadian adults 18-55 years old as two doses, 21 days apart, with three different dosages evaluated [[157](#ref-18mcJS5j4)]. This study reported that when the VLPs were administered with an adjuvant, the vaccine elicited a neutralizing antibody that was significantly (approximately 10 times) higher than that in convalescent sera [[157](#ref-18mcJS5j4)]. They also reported a cellular immune response was induced. Based on these findings, phase II and III trials began.

The findings of the phase III trial were published a few months later in the *New England Journal of Medicine* [[158](#ref-fCXfAe10)]. This study examined 24,141 adults assigned to the treatment and control conditions at a 1:1 ratio between March and September of 2021. Participants were recruited from countries in North and South America, as well as the United Kingdom. Approximately 10,000 individuals in each condition completed both doses and were evaluated in the per-protocol population. Data was submitted by Medicago and GSK to Health Canada and the vaccine was approved for use in adults ages 18 to 65 in February 2022 [[159](#ref-1JmpfIPn)].

Plant-based expression systems such as this are relatively new [[157](#ref-18mcJS5j4)] but are likely to offer unparalleled feasibility at scale given the speed and low-cost associated with the platform [[160](#ref-kbvZWBoy)]. Additionally, it can be stored at 2 to 8°C. However, the worldwide footprint of Covifenz, and of VLP-based technologies against SARS-CoV-2 broadly, remains small, with only 1 VLP vaccine approved for distribution in 0 countries (Figure [5](#fig:vlp-distrib)). Approval and administration of Covifenz in countries outside of Canada has been limited by concerns at the WHO about ties between Medicago and the tobacco industry [[154](#ref-pxEbK2Vl),[161](#ref-aEJzXfl6)]. While other species of plants have been explored as the upstream bioreactors for plant-derived VLPs, the use of the specific species of tobacco used here increased yield dramatically [[162](#ref-11WYMWwb)]. Therefore, it may be feasible to identify other species of plants that can be used for future vaccines, but the selection of *N. benthamiana* was not arbitrary.

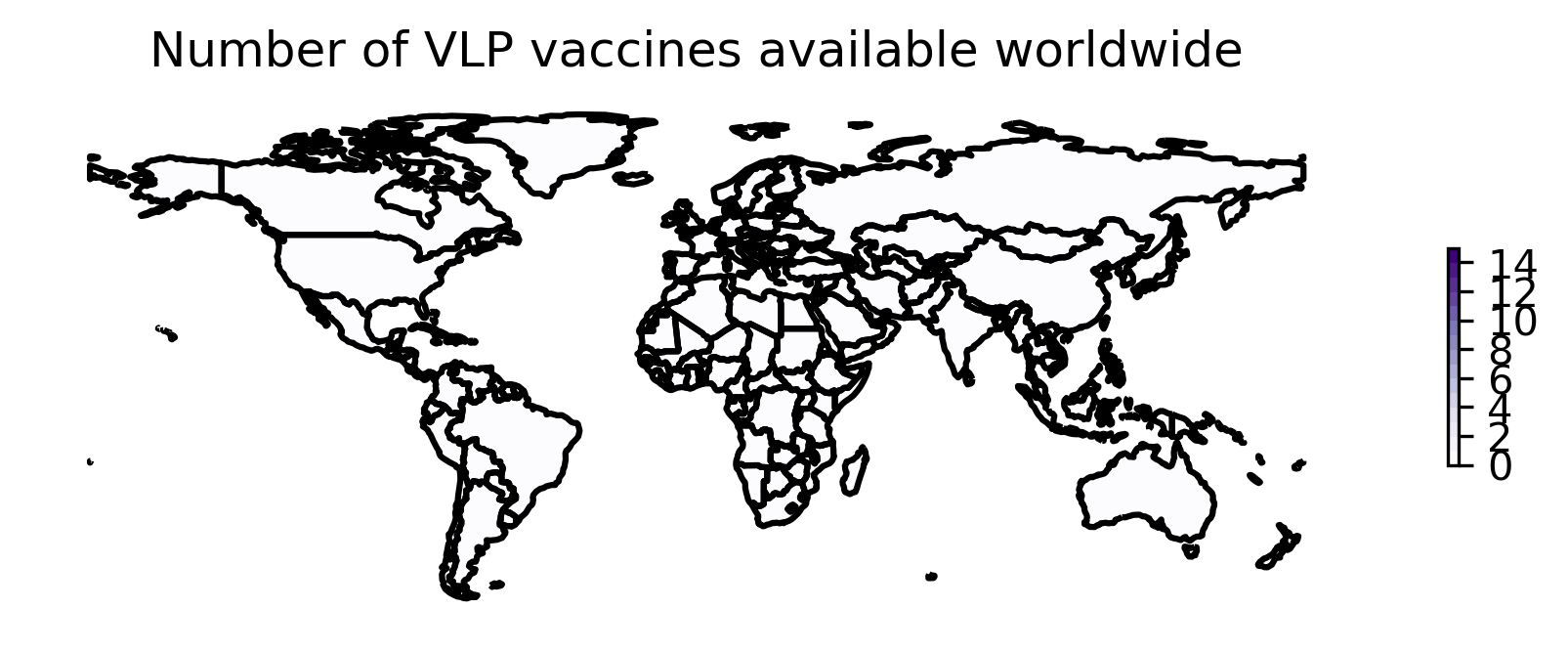


Figure 5: **Worldwide availability of vaccines developed with VLPs.** This figure reflects the number of vaccines based on VLP technology that were available in each country as of May 6, 2022. These data are retrieved from Our World in Data <!-To Do: Cite–> and plotted using geopandas. See https://greenelab.github.io/covid19-review/ for the most recent version of this figure, which is updated daily.

**Trial Safety and Efficacy:** In the phase III trial, the efficacy of Novavax was reported to be 89.7%, with a total of 10 patients developing COVID-19 in the vaccine group versus 96 in the placebo group [[150](#ref-1D0f8OrG8)]. No hospitalizations or deaths were reported in the vaccine group. An additional phase III randomized, observer-blinded, placebo-controlled trial was conducted in the U.S. and Mexico, enrolling 29,949 participants and administering at least 1 vaccine in a 2:1 ratio from late December 2020 to late February 2021 with the same primary endpoints as the U.K. trial [[163](#ref-oc5SBo0q)]. A vaccine efficacy of 90.4% was reported based on 77 cases total, 63 of which occurred in the placebo group. All moderate to severe cases of COVID-19 occurred in the placebo group. Additionally, in both trials, the vaccine was found to be well-tolerated [[150](#ref-1D0f8OrG8),[163](#ref-oc5SBo0q)]. The conclusions of both trials indicate that the NVX-CoV2373 vaccine is safe and effective against COVID-19, and those who received this vaccine through the trials are considered fully vaccinated [[164](#ref-1COb5Edqu)].

Similarly, Covifenz was reported to be 71% effective in preventing COVID-19 in the per-protocol analysis [[165](#ref-hZr9yVvu)]. Efficacy was only slightly lower in the intention-to-treat group at 69%. Prevention of moderate-to-severe disease was estimated at 78.8% in the intention-to-treat group. Over 24,000 participants were included in the safety analysis, which reported that 92.3% of vaccine recipients reported local adverse events compared to 45.5% of placebo recipients, with rates for systemic adverse events at 87.3% and 65.0%, respectively. However, the AEs reported were generally mild to moderate. Only three patients (two in the vaccine group) reported grade 4 events, all after the second dose. The most common AEs were, for local events, injection site pain and, for systemic events, headache, myalgia, fatigue, and general discomfort.

**Real-World Safety and Efficacy:** To date, data about the effect of viral evolution on the efficacy of subunit vaccines has been limited. *Post hoc* analysis in the phase III trial determined that the NovaVax vaccine had an efficacy of 86.3% against the Alpha variant (identified based on the presence/absence of the 69–70del polymorphism) and 96.4% against other variants [[150](#ref-1D0f8OrG8)]. In the second phase III trial [[163](#ref-oc5SBo0q)], whole-genome sequencing was obtained from 61 of the 77 cases, and 79% of infections were identified as a VOC or VOI that had been characterized at the time of the study. Vaccine efficacy against cases caused by VOC, among which the Alpha variant was predominant (88.6%), was reported to be 92.6% [[163](#ref-oc5SBo0q)]. In late 2020, an analysis of efficacy in South African adults revealed an overall efficacy of 60.1% and a slightly lower efficacy of 50.1% against B.1.351 in particular [[166](#ref-14K1ANV1T)].

It has also been reported that Novavax initiated booster trials in the U.K. [[72](#ref-wByD9WaX)].

Because the Covifenz results are so new (May 4, 2022), limited data is available since the publication of phase III trial results [[165](#ref-hZr9yVvu)]. However, it should be noted that the Covifenz trials were conducted in 2021, at a time during which the B.1.617.2 (delta) and P.1 (gamma) variants were predominant [[165](#ref-hZr9yVvu)]. Genomic analysis of 122 out of 176 cases (165 in the per-protocol population) revealed that none of the COVID-19 cases reported were caused by the original Wuhan strain. Instead, 45.9% of cases were identified as the delta variant, 43.4% as gamma, 4.9% as alpha, and 5.8% as VOIs. Therefore, the efficacy data from this phase III trial may be lower than it would have been if the trial had occurred earlier in the course of SARS-CoV-2’s evolution given that the S glycoprotein expressed in the VLPs was isolated from a 2020 sample of SARS-CoV-2 [[165](#ref-hZr9yVvu)].

### 0.5.3 Other Concerns in Efficacy

Given the wide range of vaccines under development, it is possible that some vaccine products may eventually be shown to be more effective in certain subpopulations, such as children, pregnant women, immunocompromised patients, the elderly, etc.

Age distribution in clinical trials? https://doi.org/10.1016/j.arr.2021.101455

Concerns: diversity of volunteer pools, variants, and distribution Another benefit of vaccines is lower population size in SARS-CoV-2 = less risk of VOC emerging that are less susceptible to the vaccine

Given the apparent need for boosters, interest has also emerged in whether vaccines against SARS-CoV-2 can be administered along with annual flu vaccines. Early data came from the Novavax NVX-CoV2373 protein subunit vaccine. In a subgroup of approximately 400 patients enrolled from the U.K. phase III trial who received either NVX-CoV2373 or placebo 1:1, a concomitant dose of adjuvanted seasonal influenza vaccines (either a trivalent vaccine or a quadrivalent vaccine) was administered [[167](#ref-IUekaKY0)]. This study demonstrated that both types of vaccines could be safely administered together. While no change to the immune response was noted for the influenza vaccine, a notable reduction of the antibody response for the NVX-CoV2373 was reported, but efficacy was still high at 87.5% [[167](#ref-IUekaKY0)]. Novavax has since started phase I/II trials to investigate the administration of its own influenza vaccine, NanoFlu™, concomitantly with NVX-CoV2373 [[168](#ref-rclKBvtk)], which appeared to be safe and effective in preclinical studies [[169](#ref-bOwPRh6q)].

Indeed, Chinese [[103](#ref-9oJ3sbrk)] and Chilean [[170](#ref-uPt61a0E)] researchers have opted to investigate options to administer different vaccines (e.g., an mRNA vaccine dose) as a booster dose to individuals who have already received two doses of the IWV vaccine CoronaVac. Another study has already determined that using the CanSino vaccine (Convidecia) instead of CoronaVac in a prime-boost vaccination regimen can induce a more robust immune response [[105](#ref-1HVWY0Qmv)]. ### Conclusions

In the early 2000s, technologies such as inactivated viral vaccines, live attenuated viral vaccines, protein subunit vaccines, and recombinant vector-based vaccines were explored for SARS [[171](#ref-H4USOXie),[172](#ref-AOGjkjCq)], but the epidemic was controlled before these efforts came to fruition [[4](#ref-HyYY2agc)]. DNA vaccine development efforts also began but did not proceed past animal testing [[172](#ref-AOGjkjCq)]. Similarly, viral vector, protein subunit, and DNA vaccines were explored for MERS-CoV, but outbreaks are sporadic and difficult to predict, making vaccine testing and the development of a vaccination strategy difficult [[173](#ref-138O0v19T)]. Likewise, the development of viral-vectored Ebola virus vaccines was undertaken, but the pace of vaccine development was behind the spread of the virus from early on [[174](#ref-vTrIB9zS)]. Although a candidate Ebola vaccine V920 showed promise in preclinical and clinical testing, it did not receive breakthrough therapy designation until the summer of 2016, by which time the Ebola outbreak was winding down [[175](#ref-8uuVgxzA)].

# 1 Additional Items

## 1.1 Competing Interests

| Author | Competing Interests | Last Reviewed |
| --- | --- | --- |

## 1.2 Author Contributions

| Author | Contributions |
| --- | --- |

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