Application of Traditional Vaccine Development Strategies to SARS-CoV-2

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## 0.1 Abstract

Over the past 150 years, vaccines have revolutionized the relationship between people and disease. Technologies such as mRNA vaccines have received significant attention due to their novelty. However, more traditional vaccine development platforms have also been explored against the virus, yielding important tools in the worldwide fight against SARS-CoV-2.

A variety of approaches have been used to develop COVID-19 vaccines that are now available in at least one country. In particular, in this review we highlight strategies that focus on the virus and its constituent pieces. Such approaches broadly fall into two categories: whole-virus vaccines and subunit vaccines. Whole-virus vaccine approaches use the virus itself, either in an inactivated or attenuated state. Subunit vaccines isolate an immunogenic component of the vaccine using various strategies that is then introduced through vaccination. We highlight specific vaccine candidates that utilize these approaches in different ways. In a companion manuscript, we review the more recent and novel development of nucleic-acid based vaccine technologies.

We also seek to contextualize the role that these COVID-19 vaccine development programs have played in providing immunity to people around the world. Well-established vaccine technologies are especially important because of their significant impact worldwide on COVID-19 vaccine access. Traditional vaccine development programs have been undertaken in a much wider range of countries than those using nucleic-acid-based technologies, which have been led by wealthy countries. Therefore, these vaccines, while less cutting-edge on the biotechnology side, are extremely important to the management of SARS-CoV-2.

## 0.2 Importance

As of May 6, 2022, SARS-CoV-2 has infected over 516,758,993 and taken the lives of at least 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. Much emphasis has been placed on vaccines that use cutting-edge biotechnology. However, more traditional methods of vaccine development that were refined throughout the twentieth century are critical to producing vaccines that are accessible worldwide. Effective deployment is critical to reducing the susceptibility of worldwide populations, especially in light of emerging variants. This review examines well-established vaccine technologies and how they are being applied to the challenges of COVID-19 at the global scale.

## 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 approaches to vaccines have been developed and refined [[1](#ref-YY3x3bBV)]. The COVID-19 pandemic has encountered several unique circumstances, one of which is the extremely rapid release of the SARS-CoV-2 viral genome. This genomic information has been important in shaping the biomedical response to this pathogen [[2](#ref-GdZc4Yyd),[3](#ref-njpLhBui)]. However, vaccines have been developed since long before the concept of a virus or viral genomes was known. As early as September 2020, there were over 180 vaccine candidates against SARS-CoV-2 in development, many of which used more traditional vaccine technologies [[4](#ref-dqpEe5Lz)]. However, media attention has largely focused on vaccine development platforms that have produced vaccine candidates using previously unemployed technologies, especially mRNA vaccines. We review vaccine technologies used for SARS-CoV-2 in two parts: here, the application of traditional vaccine development platforms to SARS-CoV-2, and separately, omics-based approaches.

Vaccine development using well-established technologies is important for a global perspective on COVID-19. As of May 6, 2022, 38 SARS-CoV-2 vaccines have been approved 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 requirements for developing and deploying a vaccine are complex and often require coordination between government, industry, academia, and philanthropic entities [[5](#ref-plfPrQP7)], and the Coalition for Epidemic Preparedness Innovations (CEPI) is coordinating global health agencies and pharmaceutical companies to develop vaccines against SARS-CoV-2.



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 [[6](#ref-14FBejgLM)] and the microscopy was conducted by the National Institute of Allergy and Infectious Diseases [[7](#ref-Jzj97hJh)].

Determining the efficacy of a vaccine is a complex question. Vaccine developers often test for serum neutralizing activity, as this has been proposed as a biomarker for adaptive immunity in other respiratory illnesses [[8](#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 3 trials where the effect of the vaccines on a cohort’s likelihood of contracting SARS-CoV-2 is evaluated, and efficacy estimates have been released for many vaccine candidates across a number of technology types based on phase 3 trial data.

However, efficacy is not a static value, and real-world efficacy can vary with location and over time. Temporal shifts in efficacy have been a especially heightened topic of concern in late 2021 given the potential for the evolution of SARS-CoV-2 to influence vaccine efficacy. Due to viral evolution, vaccine developers are in an arms race with a pathogen that benefits from mutations that reduce its susceptibility to adaptive immunity. The evolution of several variants of concern (VOC) presents significant challenges for vaccines developed based on the index strain identified in Wuhan in late 2019. We discuss these variants in depth elsewhere [[9](#ref-17qiILENK)]. To date, the most significant variants of concern identified are alpha (2020), beta (2020), gamma (2020), delta (2021) and omicron (2021). The efficacy of vaccines in the context of these variants is discussed where information is available.

## 0.4 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 [[10](#ref-Q10m9bJ),[11](#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 [[10](#ref-Q10m9bJ),[11](#ref-1Clt2Bek3),[12](#ref-ZUHALvLg),[13](#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 [[12](#ref-ZUHALvLg),[14](#ref-kC2tx3JC),[15](#ref-K0Ltu31S)]. As of 2005, most vaccines still used whole-virus platforms [[16](#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.

#### 0.4.0.1 Live-Attenuated Virus Vaccines

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 [[4](#ref-dqpEe5Lz)]. Whether variolation is the first example of a live-attenuated virus (LAV) being used to induce immunity is debated [[1](#ref-YY3x3bBV),[14](#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),[12](#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 [[4](#ref-dqpEe5Lz)]. Foreign antigens can also be integrated into an attenuated viral vector [[17](#ref-4RuaSyLg)]. LAVs are also favored because they tend to be restricted to viral replication in the tissues around the location of inoculation [[18](#ref-iX8wXLPW)], and some can be administered intranasally [[4](#ref-dqpEe5Lz)].

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 [[18](#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 [[19](#ref-wZ2tXSUH)]. There were attempts to develop LAVs against both SARS-CoV-1 and MERS-CoV [[20](#ref-7RHpaAHu)], but no vaccines were approved.

#### 0.4.0.2 Application to COVID-19

LAVs have not been widely deployed against SARS-CoV-2 and COVID-19. All the same, there are several COVID-19 LAV candidates in the early (preclinical/phase I) stages of investigation. These candidates utilize different approaches.

One candidate in the preclinical stage is YF-S0, a single-dose LAV developed at Katholieke Universiteit Leuven that uses live-attenuated yellow fever 17D (YF17D) as a vector for a noncleavable prefusion conformation of the SARS-CoV-2 antigen [[17](#ref-4RuaSyLg)]. YF-S0 induced a robust immune response in three animal models and prevented SARS-CoV-2 infection in macaques and hamsters [[17](#ref-4RuaSyLg)].

Other programs are exploring the development of codon deoptimized LAV [[21](#ref-nwyfEEPl),[22](#ref-iCUWeMfX),[23](#ref-xMxJTYge)]. This approach followed the synthetic attenuated virus engineering (SAVE) strategy to select codon substitutions that are suboptimal for the virus [[23](#ref-xMxJTYge),[24](#ref-Gnk3ge6D)]. New York-based Codagenix and the Serum Institute of India reported a successful preclinical investigation [[23](#ref-xMxJTYge)] of an intranasally administered deoptimized SARS-CoV-2 LAV known as COVI-VAC, and COVI-VAC entered phase I human trials and dosed its first participants in January 2021 [[22](#ref-iCUWeMfX),[25](#ref-bPMpOwp8)]. This vaccine is optimized through the removal of the furin cleavage site (see [[2](#ref-GdZc4Yyd)] for a discussion of this site’s importance) and deoptimization of 283 codons [[26](#ref-2VWtlcwJ)]. It is anticipated that the COVI-VAC phase I human trials will be completed by May 2022.

Another company, Meissa Vaccines in Kansas, U.S.A., which also develops vaccines for Respiratory syncytial virus (RSV), has developed an intranasal live-attenuated chimeric vaccine. Chimeric vaccines integrate genomic content from multiple viruses to create a more stable LAV [[27](#ref-14GSJSuHC)]. Enrollment for phase I human trials began in March 2021 and recruitment is ongoing [[22](#ref-iCUWeMfX),[28](#ref-8ZMg94iW)].

Finally, Bacillus Calmette-Guerin (BCG) vaccines that use LAVs are being investigated for the prophylaxis of COVID-19 (see Appendix). The purpose of the BCG vaccine is to prevent tuberculosis, but non-specific effects against other respiratory illnesses have suggested a possible benefit against COVID-19 [[29](#ref-1CJtdlM6d)]. 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 [[30](#ref-eHrzWQ6D)]. Despite these negative findings, BCG vaccination did induce a stronger antibody and cytokine response following COVID-19 infection. Currently, investigations of BCG vaccines against COVID-19 are being sponsored by institutes in Australia in collaboration with the Bill and Melinda Gates Foundation [[31](#ref-9m3rP633)] and by Texas A&M University in collaboration with numerous other U.S. institutions [[32](#ref-xdqxBruc)].

All the same, results from LAV trials in humans are largely unavailable, and no LAV vaccines are being administered at present. Despite the long and trusted history of LAV development, this vaccine strategy has not been favored against COVID-19, as other technologies have shown greater expediency and safety compared to the time-consuming nature of developing LAVs for a novel virus.

#### 0.4.0.3 Trial 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 [[33](#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 [[14](#ref-kC2tx3JC),[20](#ref-7RHpaAHu),[34](#ref-zLL2yOJK)]. Additional data are needed to ascertain how this technology performs in the case of SARS-CoV-2.

#### 0.4.0.4 Response to VOC

While no phase 3 trial data is available for LAV vaccine candidates, some manufacturers have proactively sought to respond to the emergence of VOC. For example, a poster reported that Syrian golden hamsters who received COVI-VAC were significantly less likely to lose weight following viral challenge with the Beta VOC [[26](#ref-2VWtlcwJ)]. Additionally, the protective effect of YF-S0 against VOC has been investigated in hamsters [[35](#ref-z1FVz33g)]. Even for a small number of hamsters that developed breakthrough infections after exposure to the index strain or the alpha variant, viral loads were very low [[35](#ref-z1FVz33g)]. However, much higher rates of breakthrough infection and higher viral loads were observed when the hamsters were exposed to the beta variant [[35](#ref-z1FVz33g)]. Reduced seroconversion and nAb titers were also observed against the beta and gamma variants [[35](#ref-z1FVz33g)]. As a result, a modified version of YF-S0, called YF-S0*, was developed to include a modified spike protein designed to be more immunogenic through the inclusion of the full spectrum of amino acids found in the gamma VOC as well as stabilizing the conformation [*[*35*](#ref-z1FVz33g)*]. No breakthrough infections were observed following vaccination with YF-S0 and exposure to the index strain and the alpha, beta, gamma, and delta variants [*[*35*](#ref-z1FVz33g)*]. YF-S0* also reduced viral shedding for several VOC relative to YF-S0 [[35](#ref-z1FVz33g)], and it was also observed to produce significantly more nAbs against the omicron variant [[35](#ref-z1FVz33g)]. Therefore, while data from human studies are not available, preclinical results suggest that LAV vaccines likely confer some protection against VOC even when designed with the index strain, and that modifications to the design may make this protection more robust as SARS-CoV-2 evolves.

### 0.4.1 Inactivated Whole-Virus Vaccines

Inactivated whole-virus (IWV) vaccines are another well-established vaccine platform. 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 [[36](#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 [[37](#ref-7Knbo28h)]. Additionally, the array of epitopes on the surface of the virus increases antibody binding efficiency [[37](#ref-7Knbo28h)]. The native conformation of the surface proteins, which is also important for eliciting an immune response, is preserved using these techniques [[38](#ref-10peSXMZx)]. Membrane proteins, which support B-cell responses to surface proteins, are also induced by this method [[39](#ref-iAa7uWOm)].

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 [[20](#ref-7RHpaAHu)], although this has not been the case for the COVID-19 pandemic.

Past applications to human coronaviruses (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 [[38](#ref-10peSXMZx),[40](#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 [[41](#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 [[42](#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 [[43](#ref-ZXAfLbxM)]. Independent studies in mice also demonstrated evidence of lung immunopathology due to VADE in response to MERS-CoV IWV vaccination [[44](#ref-ihrfEtMq),[45](#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 [[42](#ref-4AwyoMvQ)].

#### 0.4.1.1 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 [2](#fig:iwv-distrib)).

Table 1: Inactivated whole-virus vaccines approved in at least one country [[46](#ref-jswAyWIs)] as of May 6, 2022

| 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 |

One, CoronaVac, was developed by Beijing-based biopharmaceutical company Sinovac. The developers inactivated a SARS-CoV-2 strain collected in China with β-propiolactone and propagated it using Vero cells [[20](#ref-7RHpaAHu)]. The vaccine is coupled with an aluminum adjuvant to increase immunogenicity [[20](#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 [[47](#ref-Ozya5HP5),[48](#ref-14fILrRWg),[49](#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 [[50](#ref-1A5wiKQAW)]. Results from a two-dose phase III trial following a 14-day prime boost became available in late 2020 [[51](#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 [[52](#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]. As of August 2021, Sinovac had reportedly produced over a billion doses of CoronaVac [[53](#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. One, the BBIBP-CorV vaccine, was developed in Beijing using the HB02 strain of SARS-CoV-2. At Sinopharm CNBG’s Wuhan Institute, a second vaccine was developed using the WIV04 strain of SARS-CoV-2 [[54](#ref-miMRIMwa)]. The viruses were purified, propagated using Vero cells, isolated, and inactivated using β-propiolactone [[54](#ref-miMRIMwa),[55](#ref-VlnLw2HV)]. Both vaccines are adjuvanted with aluminum hydroxide [[54](#ref-miMRIMwa),[55](#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 [[55](#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 [[56](#ref-T3MYavsH)], with similar findings reported in interim phase II data [[56](#ref-T3MYavsH)].

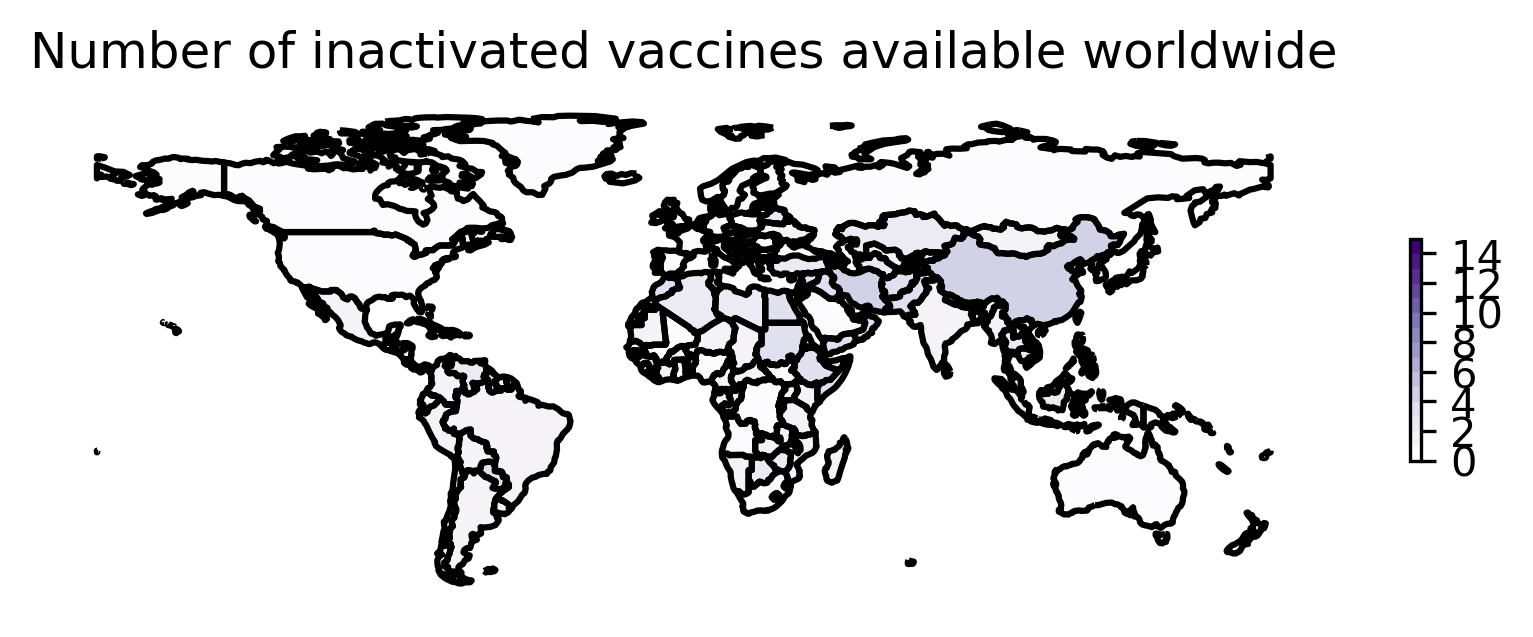


Figure 2: **Worldwide availability of vaccines developed using inactivated whole viruses.** This figure reflects the number of vaccines based on whole inactivated virus technology that were available in each country as of May 6, 2022. These data are retrieved from Our World in Data [[57](#ref-3cPwqjhj)] and plotted using geopandas [[58](#ref-nitcZF0s)]. 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 [[59](#ref-bcGxW9fA)] and macaques [[60](#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 [[61](#ref-CGuGeB7m),[62](#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 [[63](#ref-19tYVbg8H)].

#### 0.4.1.2 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 [[49](#ref-N1txjPtt)]. In older adults, the most common local and systemic reactions were pain at the injection site (9%) and fever (3%), respectively [[47](#ref-Ozya5HP5)]. In phase III trials, minimal side effects were reported [[51](#ref-1FF7JOwSH)]. For COVAXIN, only mild to moderate side-effects reported upon immunization [[61](#ref-CGuGeB7m),[62](#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 [[64](#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 [[47](#ref-Ozya5HP5)], causing the trial to be halted for investigation [[65](#ref-aq22z8M7)]. They were determined to be unrelated to the vaccine [[47](#ref-Ozya5HP5)]; [[65](#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 [[66](#ref-d09adg1G)], but this was later deemed unrelated to the vaccine, and the trial continued [[67](#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 3 trials, Sinopharm CNBG’s BBIBP-CorV vaccine made from the WIV04 strain achieved an efficacy of 72.8% and was well tolerated [[68](#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) [[69](#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 [[70](#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% [[71](#ref-18mREgqUz),[72](#ref-V7MXd4X4)]. Subsequently, an interim analysis of the phase 3 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 [[51](#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 [[73](#ref-q2wQJULu)]. Therefore, it is difficult to ascribe a particular efficacy to these vaccines given the variation in reports.

#### 0.4.1.3 Real-World Safety and Efficacy

In the past, problems that arose during the manufacturing of IWV vaccines could present safety problems, but oversight of the manufacturing process has helped to improve IWV vaccine safety [[74](#ref-1Fybz4oKI)]. Nevertheless, the departure from norms necessitated by the COVID-19 crisis raised concerns about whether oversight would occur at pre-pandemic standards [[74](#ref-1Fybz4oKI)]. In general, the IWV COVID-19 vaccines have reported very few issues with safety. Additionally, safety audits have proactively identified concerns. For example, in April 2022, the WHO suspended procurement of Covaxin from Bharat Pharmaceuticals due to concerns about deviation from good manufacturing practice in their production facilities [[75](#ref-19hWVUQQ)]. However, no safety issues had been reported in association with this vaccine. Rare cases of VADE have been reported in association with CoronaVac [[76](#ref-14KuNOjDi)].

More concern has arisen around the issue of 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 [[15](#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 [[77](#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) [[78](#ref-lr7INjf6),[79](#ref-UYE3NvU4),[80](#ref-IvOEe7bV)], the phase III trial reported a 65.2% efficacy against the delta variant (B.1.617.2) [[69](#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 [[77](#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) [[78](#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) [[81](#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 [[82](#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 [[77](#ref-s2O5iyCV)]. The authors noted that no evidence of VADE was detected using this vaccine in phase II data [[56](#ref-T3MYavsH)].

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 [[83](#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 [[84](#ref-1GcPxd9Bn)] and COVAXIN [[85](#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 [[86](#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 [[87](#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 [[88](#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 [[53](#ref-wByD9WaX)]. Additionally, heterogeneous vaccine boosters are also being considered in many cases. Indeed, Chinese [[89](#ref-9oJ3sbrk)] and Chilean [[90](#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 determined that using a viral-vectored vaccine (CanSino’s Convidecia) or an mRNA vaccine (Pfizer/BioNTech’s BNT162b2) instead of CoronaVac in a prime-boost vaccination regimen could induce a more robust immune response [[91](#ref-1HVWY0Qmv),[92](#ref-hcnFsRig),[93](#ref-1Cd41ucny)]. Chinese [[89](#ref-9oJ3sbrk)] and Chilean [[94](#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 [[91](#ref-1HVWY0Qmv)]. Today, booster immunization is suggested for several whole-virus vaccines.

## 0.5 Subunit Vaccines

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),[95](#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 [[96](#ref-99C1xJ2E)].

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 [[97](#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 [[98](#ref-1Bxg7Wj6w)]. Protein subunit vaccines can stimulate antibodies and CD4+ T-cell responses [[99](#ref-12eGVhH5I),[100](#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 [[101](#ref-124bnGvPp)]. The immune response generated by protein subunit vaccines is weaker, and adjuvants are usually required to boost the response [[102](#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 [[101](#ref-124bnGvPp),[103](#ref-rioTBsLc)].

Table 2: Approved subunit vaccines [[46](#ref-jswAyWIs)] as of May 6, 2022

| 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 |

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 [[104](#ref-cLAQnckq),[105](#ref-1EirBATaN),[106](#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 [[107](#ref-Ow2ICHez),[108](#ref-tzZeWNPV)], those focused on the RBD protein only [[104](#ref-cLAQnckq),[105](#ref-1EirBATaN),[106](#ref-1AOG59epD),[109](#ref-DsfTQFmb)] or non-RBD S protein fragments [[108](#ref-tzZeWNPV),[110](#ref-IYjNaaqv)], as well as the N and M proteins [[111](#ref-HvO79P9u),[112](#ref-VUcwpJKL),[113](#ref-7hbgOaiE)]; these efforts have been thoroughly reviewed elsewhere [[114](#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 [[115](#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 [[116](#ref-GurQD2dO)], but these responses were not as effective as the combination of S DNA and the S1 subunit protein together [[116](#ref-GurQD2dO),[117](#ref-T7W7hnB9)].

Similarly to the SARS-CoV-1 vaccine candidates, the MERS-CoV protein subunit vaccine candidates generally target the RBD [[105](#ref-1EirBATaN),[114](#ref-9Zv0eLa9),[118](#ref-Mki0DaYb),[119](#ref-aApaHV1w),[120](#ref-deUFGhNI),[121](#ref-sfM5QV3m)], with some targeting the full length S protein [[122](#ref-oghHqZDt)], non-RBD protein fragments such as the SP3 peptide [[123](#ref-11Zz9H0Dl)], and the recombinant N-terminal domain (rNTD) [[124](#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 [[125](#ref-oqty7gXw),[126](#ref-eHe78HXD)] including testing in animal models [[127](#ref-cnYnzav2),[128](#ref-G87TcArN)], but once again, only preclinical data against HCoV has been collected [[129](#ref-jLJEygoA)]. However, protein subunit vaccines do play a role in public health and have contributed to vaccination against hepatitis B [[130](#ref-155fGivMy)] and pertussis [[131](#ref-CQog2bB7),[132](#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 [[133](#ref-1FQlt5Lqz),[134](#ref-8dSIiLCt),[135](#ref-aAYBP21H)].

#### 0.5.0.1 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 [[134](#ref-8dSIiLCt)] and 15 are being administered worldwide [[136](#ref-cWMPXfju)]. VLP vaccines have not progressed as rapidly, with only 1 VLP vaccines approved [[134](#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 [[97](#ref-1FfwyYaj7)]. As of March 30, 2022, 14 protein subunit vaccines are being distributed in 21 countries (Figure 4).

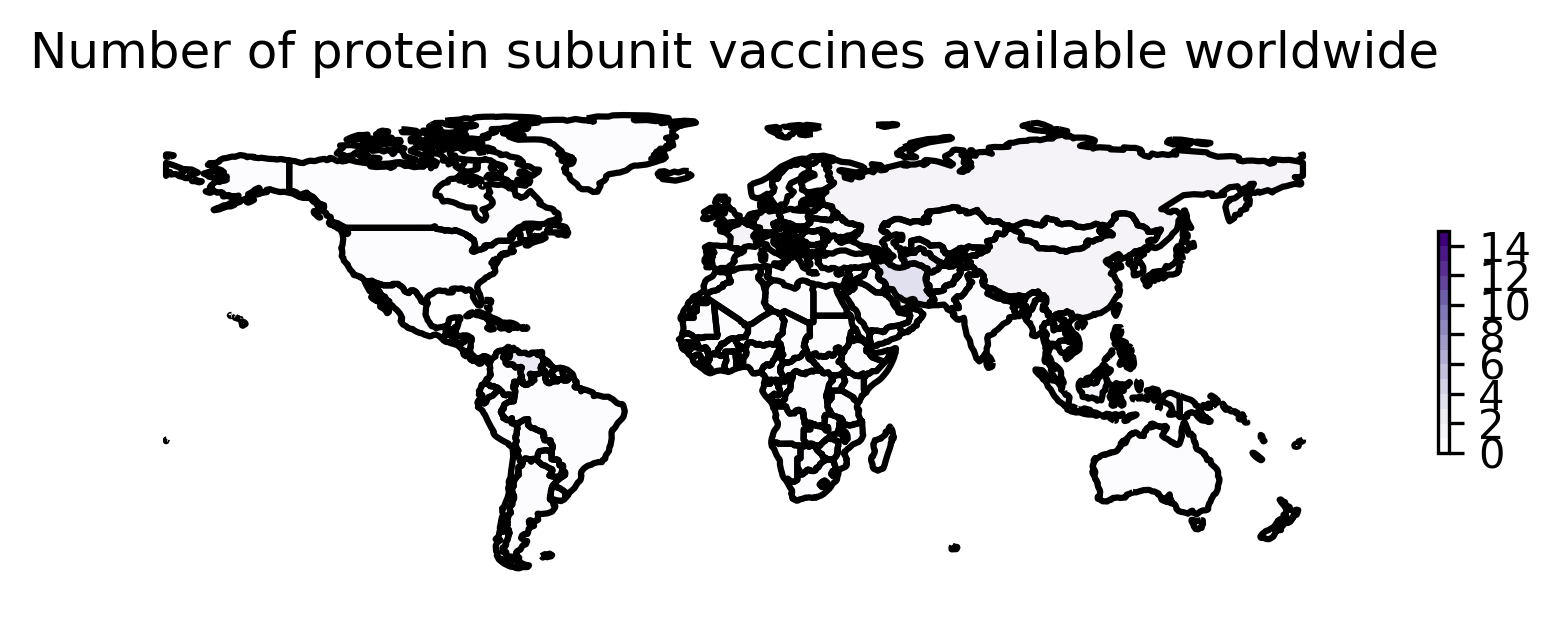


Figure 3: **Worldwide availability of vaccines developed using protein subunit.** This figure reflects the number of vaccines based on protein subunit technology that were available in each country as of May 6, 2022. These data are retrieved from Our World in Data [[57](#ref-3cPwqjhj)] and plotted using geopandas [[58](#ref-nitcZF0s)]. 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 [[137](#ref-Qk33ZrIC)], which have previously been used for several other FDA-approved protein therapeutics [[138](#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 [[137](#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 [[137](#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 [[139](#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 [[140](#ref-1D0f8OrG8)]. Novavax has since been approved in several places, including the United Kingdom [[141](#ref-q3wIcP4d)] and the E.U. [[142](#ref-P3YhxRob)], and the company applied for an EUA from the FDA in early 2022 [[143](#ref-6mHA0NU9)]. Novavax has also signed agreements with the U.K., Canada, Australia, and South Korea [[144](#ref-X3fVa3P8)] and has projected that they will supply 1.1 billion doses to COVAX who will distribute the vaccines to countries with disadvantaged access to vaccine supplies [[53](#ref-wByD9WaX)]. However, as of May 2022, the vaccine has yet to be authorized in the United States, after encountering many delays in manufacturing [[145](#ref-ORkwMcrn)].

The leading example of a VLP approach applied to COVID-19 comes from Covifenz, a VLP vaccine developed by Canadian company Medicago [[146](#ref-pxEbK2Vl)]. This vaccine was developed using plant-based VLP technology [[147](#ref-18Xmc8WMR)] that the company had been investigating in order to develop a high-throughput quadrivalent VLP platform to provide protection against influenza [[148](#ref-WqqE64cZ)]. The approach utilizes *Nicotiana benthamiana*, an Australian relative of the tobacco plant, as an upstream bioreactor [[148](#ref-WqqE64cZ),[149](#ref-18mcJS5j4),[149](#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 [[148](#ref-WqqE64cZ),[149](#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 [[149](#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 [[148](#ref-WqqE64cZ),[149](#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 [[149](#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 [[149](#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* [[150](#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 [[151](#ref-1JmpfIPn)].

Plant-based expression systems such as this are relatively new [[149](#ref-18mcJS5j4)] but are likely to offer unparalleled feasibility at scale given the speed and low-cost associated with the platform [[152](#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 [4](#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 [[146](#ref-pxEbK2Vl),[153](#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 [[154](#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.

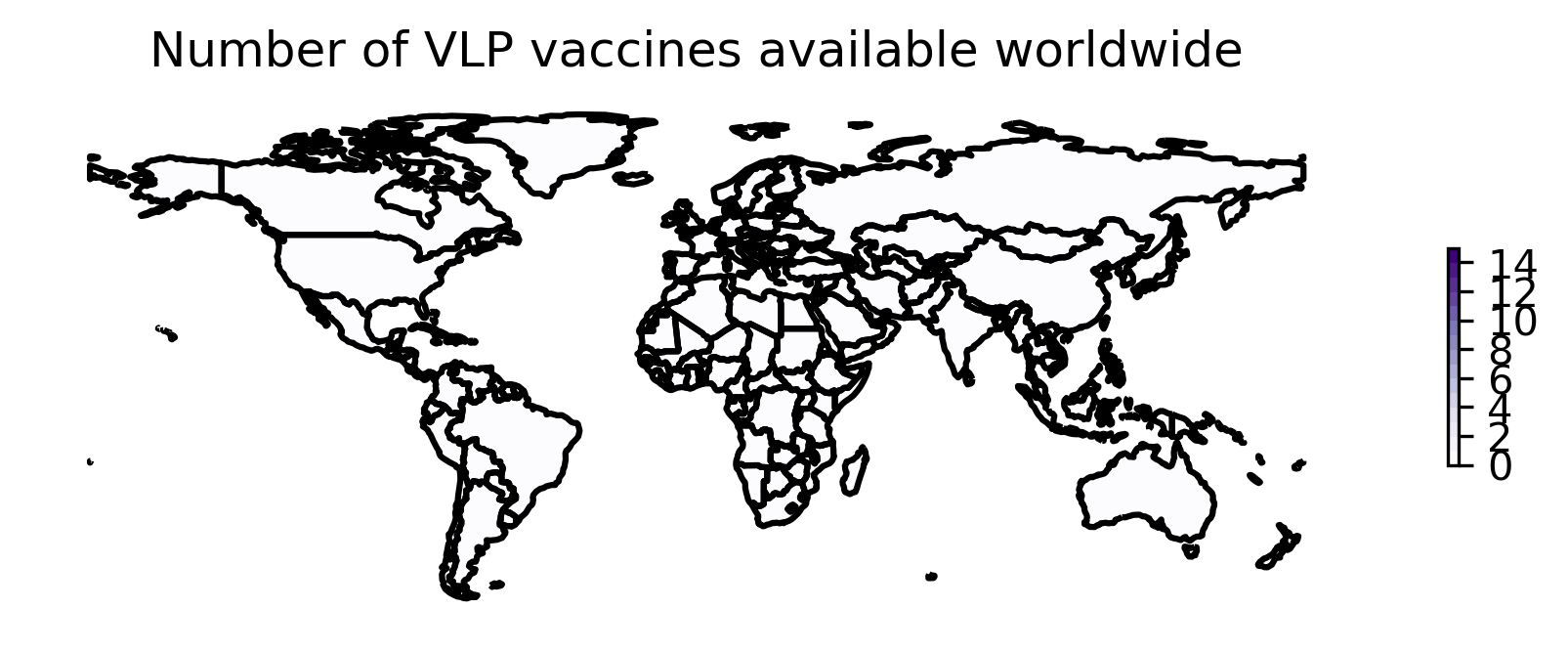


Figure 4: **Worldwide availability of vaccines developed with VLPs.** This figure reflects the number of vaccines based on VLP technology that were available in each country as of May 6, 2022. These data are retrieved from Our World in Data [[57](#ref-3cPwqjhj)] and plotted using geopandas [[58](#ref-nitcZF0s)]. See https://greenelab.github.io/covid19-review/ for the most recent version of this figure, which is updated daily.

#### 0.5.0.2 Trial Safety and Efficacy

In the phase 3 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 [[140](#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 [[155](#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 [[140](#ref-1D0f8OrG8),[155](#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 [[156](#ref-1COb5Edqu)].

Similarly, Covifenz was reported to be 71% effective in preventing COVID-19 in the per-protocol analysis [[157](#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.

#### 0.5.0.3 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 [[140](#ref-1D0f8OrG8)]. In the second phase III trial [[155](#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% [[155](#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 [[158](#ref-14K1ANV1T)]. Additionally, an analysis of a booster dose of NVX-CoV2373 administered six months after the primary series revealed a significant increase in neutralizing activity of VOC including delta and omicron [[159](#ref-S28ZsPCI)]. It has also been reported that Novavax initiated booster trials in the U.K. [[53](#ref-wByD9WaX)].

Because the Covifenz results are so new (May 4, 2022), limited data is available since the publication of phase III trial results [[157](#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 [[157](#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 3 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 [[157](#ref-hZr9yVvu)].

## 0.6 Global Vaccine Status and Distribution

The unprecedented deployment of COVID-19 vaccines in under a year from the identification of SARS-CoV-2 led to a new challenge: the formation of rapid global vaccine production and distribution plans. The development of vaccines is costly and complicated, but vaccine distribution can be just as challenging. Logistical considerations such as transport, storage, equipment (e.g., syringes), the workforce to administer the vaccines, and a continual supply from the manufacturers to meet global demands all must be accounted for and will vary globally due to economic, geographic, and sociopolitical reasons [[160](#ref-RG0vzlcE),[161](#ref-19CWe6pdS),[162](#ref-d0kUYq5Z)]. As of May 6, 2022, approximately 12 billion vaccine doses have been administered in at least 223 countries worldwide using 27 different vaccines [[57](#ref-3cPwqjhj)]. The daily global vaccination rate is currently 1,113 per million.

However, the distribution of these doses is not uniform around the globe. Vaccination rates are lower in South America (3.1 per 100), Asia (1.9 per 100), Africa (0.3 per 100), and Oceania (0.1 per 100) than in North America, Europe, and Australia [[163](#ref-dfl5iCJI)]. Vaccine production and distribution varies from region to region and seems to depend on the availability of the vaccines and potentially a country’s resources and wealth [[164](#ref-kL8PlRJu)]. One effort to reduce these disparities is the COVID-19 Vaccines Global Access (COVAX) Facility, a multilateral initiative as part of the Access to COVID-19 Tools (ACT) Accelerator coordinated by the WHO, Gavi The Vaccine Alliance, and the Coalition for Epidemic Preparedness Innovations (CEPI), the latter two of which are supported by the Bill and Melinda Gates Foundation. Their intention is to accelerate the development of COVID-19 vaccines, diagnostics, and therapeutics and to ensure the equitable distribution of vaccines to low- and middle-income countries [[165](#ref-3Gq7ETv7),[166](#ref-KzHIbPMY)]. COVAX invested in several vaccine programs to ensure they would have access to successful vaccine candidates [[167](#ref-1H0PiQpLz)].

Additionally, the vaccine technologies available differ widely around the globe. As we review elsewhere, wealthier nations have invested heavily in mRNA and DNA vaccines. In contrast, as we describe above, many countries outside of Europe and North America have developed highly effective vaccines using more traditional approaches.

### 0.6.1 Asia

The Asian nations of China and India have played a major role as COVID-19 vaccination developers and providers. India has vaccinated approximately 24 million people [[168](#ref-DQmAgN0V)]. and shipped approximately 58 million COVID-19 vaccines to 66 countries [[169](#ref-QRYET3sK)].

Considering India produces approximately 60% of the world’s vaccines prior to the pandemic, it is no surprise that several COVID-19 vaccine candidates are under development. In addition to COVAXIN, the Bio E subunit vaccine CORBEVAX is being produced by Biological E in collaboration with U.S.-based Dynavax and the Baylor College of Medicine [[170](#ref-gsNWcXHn)]. These two home-grown vaccines are now approved for adults and children as young as five (CORBEVAX) and six (COVAXIN) [[171](#ref-I9Ha5JL3)].

Other vaccines licensed by India were developed elsewhere but produced in India. For example, Novavax (developed in the United States) has signed an agreement with the Serum Institute of India allowing them to produce up to 2 billion doses a year [[172](#ref-e8pnj0O3)]. Similarly, many people within India have been vaccinated with the AstraZeneca-University of Oxford vaccine, known as Covishield in India, which is also produced by the Serum Institute of India [[170](#ref-gsNWcXHn)].

India is also developing vaccines using cutting-edge nucleic-acid-based platforms. These include ZyCov-D, a DNA vaccine produced by Zydus Cadila, HGCO19 and India’s first mRNA vaccine, produced by Genova and HDT Biotech Corporation (of the U.S.) [[170](#ref-gsNWcXHn)]. Additionally, in February, 2021, Bharat Biotech received approval from Indian officials to commence a phase I study of an intranasal chimpanzee-adenovirus (ChAd) vectored SARS-CoV-2-S vaccine called BBV154 [[173](#ref-P9mD7Gc9)].

In China, the Sinopharm-Beijing Institute vaccine, the Sinopharm-Wuhan Institute of Biological Products vaccine, the Sinovac Biotech (CoronaVac) vaccine, and CanSino Biologics vaccine are the main vaccines being distributed. The Sinopharm-Beijing vaccine has been distributed to at least 16 countries. Indeed, Sinovac and Sinopharm have estimated that they will be able to produce 2 billion doses by the end of 2021, and they have been able to distribute vaccines as aid to the Philippines and Pakistan [[174](#ref-gdTtuj5e)]. In contrast, the Sinopharm-Wuhan vaccine, which has been approved for use in China since February 25th, 2021, has been distributed almost exclusively within China, with limited supplies distributed to the United Arab Emirates [[175](#ref-mR6133bK)]. On the same date, the CanSino vaccine was approved for use in China and has been granted emergency use in Mexico and Pakistan, which were two participating countries in the CanSino phase 3 trials [[176](#ref-4PSTgetR)].

However, the vaccine approval and distribution processes in China have come under increased scrutiny from other nations. China was criticized for administering vaccines to thousands of government officials and state-owned businesses in September 2020, prior to the completion of phase III clinical trials [[177](#ref-1Bgnim0gX)]. The behavior of Chinese officials has also come into question due to misinformation campaigns questioning the safety of Western vaccine candidates such as Moderna and Pfizer-BioNTech in a way that is intended to highlight the benefits of their own vaccine candidates [[174](#ref-gdTtuj5e)]. China in particular took aim at mRNA technologies, but Chinese companies have since developed their own mRNA vaccines targeting the Omicron variant, one of which is due to begin trials soon in the UAE [[178](#ref-V2Gz2O9G)/]. Furthermore, delays in vaccine distribution have also caused issues, particularly in Turkey where 10 million doses of Sinovac were due to arrive by December 2020, but instead only 3 million were delivered in early January [[174](#ref-gdTtuj5e)]. Similar delays and shortages of doses promised have been reported by officials in the Philippines, Egypt, Morocco, and the United Arab Emirates [[179](#ref-XJmfG8HD),[180](#ref-12zVLzkpB)]. This will be concerning to China who have vaccine contracts for millions of doses with Indonesia (>100 million), Brazil (100 million), Chile (60 million), Turkey (50 million), Egypt (40 million) and many others [[180](#ref-12zVLzkpB)].

### 0.6.2 Latin America

### 0.6.3 North America and Europe

When vaccines first became available, the wealthy nations of North America and Europe secured most of the limited COVID-19 vaccine stocks [[181](#ref-1AvwH3T5y)]. Throughout 2021, low- and middle-income countries faced steep competition with high-income countries for vaccines, and the rates of vaccination reflected this unequal distribution [[182](#ref-JM2MJEBG)]. While the wealthiest countries in these regions could compete with each other for vaccines independent of programs such as COVAX [[182](#ref-JM2MJEBG)], other countries in these regions have faced challenges in acquiring vaccines developed by the world’s wealthiest nations.

For example, in Cuba,

### 0.6.4 Africa

Following the release of the phase III data indicating 81% efficacy, Zimbabwe authorized the use of Covaxin [[183](#ref-13yEnvOyP)].

While South Africa and Zimbabwe have their own vaccination programs, many other African nations will be reliant on the COVID-19 Vaccines Global Access (COVAX) Facility, who have promised 600 million doses to the continent [[184](#ref-1EnpYQzIq)]. As of March, 2021, 9 African countries have received vaccines and at least 11 other nations have begun vaccinations via COVAX, aid from other countries, or their own agreements with producers [[184](#ref-1EnpYQzIq),[185](#ref-2b6FdDOy)]. However, much further progress is required when only 0.3 per 100 people have been vaccinated in Africa [[163](#ref-dfl5iCJI)].

## 0.7 Conclusions

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

The COVAX plan seeks to ensure that all participating countries would be allocated vaccines in proportion to their population sizes. Once each country has received vaccine doses to account for 20% of their population, the country’s risk profile will determine its place in subsequent phases of vaccine distribution. However, several limitations of this framework exist, including that the COVAX scheme seems to go against the WHO’s own ethical principles of human well-being, equal respect, and global equity, and that other frameworks might have been more suitable, as is discussed elsewhere [[186](#ref-12QaZb4si)]. Furthermore, COVAX is supposed to allow poorer countries access to affordable vaccines, but the vaccines are driven by publicly traded companies that are required to make a profit [[164](#ref-kL8PlRJu)]. In any case, COVAX provides access to COVID-19 vaccines that may otherwise have been difficult for some countries to obtain. COVAX aims to distribute 2 billion vaccine doses globally by the end of 2021 [[187](#ref-7dkwQDUf)]. COVAX may also receive additional donations of doses from Western nations who purchased surplus vaccines in the race to vaccinate their populations, which will be a welcome boost to the vaccination programs of low- and middle-income countries [[188](#ref-sr5oRBgc)].

In general, deciding on the prioritization and allocation of the COVID-19 vaccines is also a challenging task due to ethical and operational considerations. Various frameworks, models, and methods have been proposed to tackle these issues with many countries, regions or states as is the case in the U.S., devising their own distribution and administration plans [[189](#ref-S8WhufUV),[190](#ref-dLbKv1xi),[191](#ref-jbpdQdOw),[192](#ref-z5c17nGB),[193](#ref-s2zZd6pb)]. The majority of the distribution plans prioritize offering vaccines to key workers such as health care workers, and those who are clinically vulnerable such as the elderly, the immunocompromised, and individuals with comorbidities, before targeting the rest of the population, who are less likely to experience severe outcomes from COVID-19 [[194](#ref-sEyIoYCS)].

Additionally, authorization of a vaccine by a government typically requires extended discussions with vaccine manufacturers. For the United States, Australia, and United Kingdom, for example, a manufacturer must submit and present large amounts of data to committees like the FDA .

Much attention has focused on the most novel vaccine technologies that have been deployed against SARS-CoV-2. The vaccine platforms discussed here have all made a significant impact on human health during the twentieth century and in some cases even earlier. However, this does not mean that the COVID-19 pandemic has not also demonstrated new potential in these technologies. In the early 2000s, the technologies discussed here were all explored for managing SARS-CoV-1 [[195](#ref-H4USOXie),[196](#ref-AOGjkjCq)], but the epidemic was controlled before these efforts came to fruition [[197](#ref-HyYY2agc)]. Similarly, these technologies were explored for MERS-CoV, but outbreaks are sporadic and difficult to predict, making vaccine testing and the development of a vaccination strategy difficult [[198](#ref-138O0v19T)]. However, in the COVID-19 pandemic, most of these technologies have been used to accelerate vaccine development programs worldwide. Therefore, they are also offering the opportunity to respond quickly to an emergent pathogen.

While these tried-and-true technologies might not produce vaccines with quite the unprecedented levels of VE as seen in some vaccine development programs (e.g., ModernaTX and Pfizer/BioNTech’s reports of >90% VE for their mRNA vaccines), the efficacies are still generally very high, and very effective at preventing severe illness and death. As a result, it can be argued that the greater accessibility and stability of these vaccines makes them more valuable at a global level. The makers of Corbevax, a protein subunit vaccine, for example, have been nominated for a Nobel Peace Prize due to the potential for their vaccine to be produced globally [[199](#ref-JLQFduwq)].

# 1 Additional Items

## 1.1 Competing Interests

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

## 1.2 Author Contributions

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

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## 1.4 References

1. **History of vaccination** Stanley Plotkin *Proceedings of the National Academy of Sciences* (2014-08-18) <https://doi.org/f6fcwk> DOI: [10.1073/pnas.1400472111](https://doi.org/10.1073/pnas.1400472111) · PMID: [25136134](https://www.ncbi.nlm.nih.gov/pubmed/25136134) · PMCID: [PMC4151719](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4151719)

2. **Pathogenesis, Symptomatology, and Transmission of SARS-CoV-2 through Analysis of Viral Genomics and Structure** Halie M Rando, Adam L MacLean, Alexandra J Lee, Ronan Lordan, Sandipan Ray, Vikas Bansal, Ashwin N Skelly, Elizabeth Sell, John J Dziak, Lamonica Shinholster, … Casey S Greene *mSystems* (2021-10-26) <https://pubmed.ncbi.nlm.nih.gov/34698547/> DOI: [10.1128/msystems.00095-21](https://doi.org/10.1128/mSystems.00095-21)

3. **Identification and Development of Therapeutics for COVID-19** Halie M Rando, Nils Wellhausen, Soumita Ghosh, Alexandra J Lee, Anna Ada Dattoli, Fengling Hu, James Brian Byrd, Diane N Rafizadeh, Ronan Lordan, Yanjun Qi, … Casey S Greene *mSystems* (2021-12-21) <https://pubmed.ncbi.nlm.nih.gov/34726496/> DOI: [10.1128/msystems.00233-21](https://doi.org/10.1128/mSystems.00233-21)

4. **SARS-CoV-2 vaccines in development** Florian Krammer *Nature* (2020-09-23) <https://doi.org/ghdprn> DOI: [10.1038/s41586-020-2798-3](https://doi.org/10.1038/s41586-020-2798-3) · PMID: [32967006](https://www.ncbi.nlm.nih.gov/pubmed/32967006)

5. **A strategic approach to COVID-19 vaccine R&amp;D** Lawrence Corey, John R Mascola, Anthony S Fauci, Francis S Collins *Science* (2020-05-29) <https://doi.org/ggwfck> DOI: [10.1126/science.abc5312](https://doi.org/10.1126/science.abc5312) · PMID: [32393526](https://www.ncbi.nlm.nih.gov/pubmed/32393526)

6. **BioRender** BioRender <https://biorender.com/>

7. **New Images of Novel Coronavirus SARS-CoV-2 Now Available | NIH: National Institute of Allergy and Infectious Diseases** <https://www.niaid.nih.gov/news-events/novel-coronavirus-sarscov2-images>

8. **An mRNA Vaccine against SARS-CoV-2 — Preliminary Report** Lisa A Jackson, Evan J Anderson, Nadine G Rouphael, Paul C Roberts, Mamodikoe Makhene, Rhea N Coler, Michele P McCullough, James D Chappell, Mark R Denison, Laura J Stevens, … John H Beigel *New England Journal of Medicine* (2020-11-12) <https://doi.org/d3tt> DOI: [10.1056/nejmoa2022483](https://doi.org/10.1056/nejmoa2022483) · PMID: [32663912](https://www.ncbi.nlm.nih.gov/pubmed/32663912) · PMCID: [PMC7377258](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7377258)

9. **Evolutionary and Genomic Analysis of SARS-CoV-2** COVID-19 Review Consortium *Manubot* (2021-03-30) <https://greenelab.github.io/covid19-review/v/910dd7b7479f5336a1c911c57446829bef015dbe/#evolutionary-and-genomic-analysis-of-sars-cov-2>

10. **The history of the smallpox vaccine** Alexandra J Stewart, Phillip M Devlin *Journal of Infection* (2006-05) <https://doi.org/d455hw> DOI: [10.1016/j.jinf.2005.07.021](https://doi.org/10.1016/j.jinf.2005.07.021) · PMID: [16176833](https://www.ncbi.nlm.nih.gov/pubmed/16176833)

11. **“Variolation” and Vaccination in Late Imperial China, Ca 1570–1911** Angela Ki Che Leung *History of Vaccine Development* (2011) <https://doi.org/fftx2m> DOI: [10.1007/978-1-4419-1339-5\_2](https://doi.org/10.1007/978-1-4419-1339-5_2)

12. **The History Of Vaccines And Immunization: Familiar Patterns, New Challenges** Alexandra Minna Stern, Howard Markel *Health Affairs* (2005-05) <https://doi.org/dzcwg5> DOI: [10.1377/hlthaff.24.3.611](https://doi.org/10.1377/hlthaff.24.3.611) · PMID: [15886151](https://www.ncbi.nlm.nih.gov/pubmed/15886151)

13. **Equination (inoculation of horsepox): An early alternative to vaccination (inoculation of cowpox) and the potential role of horsepox virus in the origin of the smallpox vaccine** José Esparza, Livia Schrick, Clarissa R Damaso, Andreas Nitsche *Vaccine* (2017-12) <https://doi.org/gcsnbp> DOI: [10.1016/j.vaccine.2017.11.003](https://doi.org/10.1016/j.vaccine.2017.11.003) · PMID: [29137821](https://www.ncbi.nlm.nih.gov/pubmed/29137821)

14. **Live attenuated vaccines: Historical successes and current challenges** Philip D Minor *Virology* (2015-05) <https://doi.org/f7cnmj> DOI: [10.1016/j.virol.2015.03.032](https://doi.org/10.1016/j.virol.2015.03.032) · PMID: [25864107](https://www.ncbi.nlm.nih.gov/pubmed/25864107)

15. **Advances in mRNA Vaccines for Infectious Diseases** Cuiling Zhang, Giulietta Maruggi, Hu Shan, Junwei Li *Frontiers in Immunology* (2019-03-27) <https://doi.org/ggsnm7> DOI: [10.3389/fimmu.2019.00594](https://doi.org/10.3389/fimmu.2019.00594) · PMID: [30972078](https://www.ncbi.nlm.nih.gov/pubmed/30972078) · PMCID: [PMC6446947](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6446947)

16. **DNA Vaccine** Zhengrong Cui *Non-Viral Vectors for Gene Therapy, Second Edition: Part 2* (2005) <https://doi.org/dn299p> DOI: [10.1016/s0065-2660(05)54011-2](https://doi.org/10.1016/s0065-2660(05)54011-2) · PMID: [16096015](https://www.ncbi.nlm.nih.gov/pubmed/16096015) · PMCID: [PMC7119308](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7119308)

17. **A single-dose live-attenuated YF17D-vectored SARS-CoV-2 vaccine candidate** Lorena Sanchez-Felipe, Thomas Vercruysse, Sapna Sharma, Ji Ma, Viktor Lemmens, Dominique Van Looveren, Mahadesh Prasad Arkalagud Javarappa, Robbert Boudewijns, Bert Malengier-Devlies, Laurens Liesenborghs, … Kai Dallmeier *Nature* (2020-12-01) <https://doi.org/ghn8jk> DOI: [10.1038/s41586-020-3035-9](https://doi.org/10.1038/s41586-020-3035-9) · PMID: [33260195](https://www.ncbi.nlm.nih.gov/pubmed/33260195)

18. **Principles of Virology, Volume I: Molecular Biology** Jane Flint, Anna Marie Skalka, Glenn F Rall, Vincent R Racaniello *American Society of Microbiology* (2015-01-01) <https://doi.org/gmqjck> DOI: [10.1128/9781555818951](https://doi.org/10.1128/9781555818951)

19. **Vaccine Immunology** Claire-Anne Siegrist *Plotkin's Vaccines* (2018) <https://doi.org/gmqjcc> DOI: [10.1016/b978-0-323-35761-6.00002-x](https://doi.org/10.1016/b978-0-323-35761-6.00002-x)

20. **COVID-19: Coronavirus Vaccine Development Updates** Jing Zhao, Shan Zhao, Junxian Ou, Jing Zhang, Wendong Lan, Wenyi Guan, Xiaowei Wu, Yuqian Yan, Wei Zhao, Jianguo Wu, … Qiwei Zhang *Frontiers in Immunology* (2020-12-23) <https://doi.org/gkbs4k> DOI: [10.3389/fimmu.2020.602256](https://doi.org/10.3389/fimmu.2020.602256) · PMID: [33424848](https://www.ncbi.nlm.nih.gov/pubmed/33424848) · PMCID: [PMC7785583](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7785583)

21. **Griffith University researchers on the road to COVID-19 vaccine** Deborah Marshall <https://news.griffith.edu.au/2020/04/23/griffith-university-researchers-on-the-road-to-covid-19-vaccine/>

22. **Milken Institute’s COVID-19 Treatment and Vaccine Tracker tracks the development of treatments and vaccines for COVID-19 at covid-19tracker.milkeninstitute.org #COVID19 #coronavirus #COVID19treatment #COVID19vaccine @MilkenInstitute @FirstPersonSF** <https://covid-19tracker.milkeninstitute.org/>

23. **Scalable live-attenuated SARS-CoV-2 vaccine candidate demonstrates preclinical safety and efficacy** Ying Wang, Chen Yang, Yutong Song, JRobert Coleman, Marcin Stawowczyk, Juliana Tafrova, Sybil Tasker, David Boltz, Robert Baker, Liliana Garcia, … Steffen Mueller *Proceedings of the National Academy of Sciences* (2021-06-30) <https://doi.org/gmc76v> DOI: [10.1073/pnas.2102775118](https://doi.org/10.1073/pnas.2102775118) · PMID: [34193524](https://www.ncbi.nlm.nih.gov/pubmed/34193524) · PMCID: [PMC8307828](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8307828)

24. **Virus Attenuation by Genome-Scale Changes in Codon Pair Bias** JRobert Coleman, Dimitris Papamichail, Steven Skiena, Bruce Futcher, Eckard Wimmer, Steffen Mueller *Science* (2008-06-27) <https://doi.org/db9r24> DOI: [10.1126/science.1155761](https://doi.org/10.1126/science.1155761) · PMID: [18583614](https://www.ncbi.nlm.nih.gov/pubmed/18583614) · PMCID: [PMC2754401](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2754401)

25. **First-in-human, Randomised, Double-blind, Placebo-controlled, Dose-escalation Study in Healthy Young Adults Evaluating the Safety and Immunogenicity of COVI-VAC, a Live Attenuated Vaccine Candidate for Prevention of COVID-19** Codagenix, Inc *clinicaltrials.gov* (2021-07-26) <https://clinicaltrials.gov/ct2/show/NCT04619628>

26. **577. COVI-VAC™, a Live Attenuated COVID-19 Vaccine, Provides Single Dose Protection Against Heterologous Challenge with SARS-CoV-2 Beta (B.1.351) in the Syrian Golden Hamster Model** Anna Kushnir, Steffen Mueller, Sybil Tasker, J Robert Coleman *Open Forum Infectious Diseases* (2021-12-04) <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8644885/> DOI: [10.1093/ofid/ofab466.775](https://doi.org/10.1093/ofid/ofab466.775) · PMCID: [PMC8644885](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8644885)

27. **Recent Progress in Vaccine Development Against Chikungunya Virus** Shan Gao, Siqi Song, Leiliang Zhang *Frontiers in Microbiology* (2019-12-19) <https://doi.org/gh7rn6> DOI: [10.3389/fmicb.2019.02881](https://doi.org/10.3389/fmicb.2019.02881) · PMID: [31921059](https://www.ncbi.nlm.nih.gov/pubmed/31921059) · PMCID: [PMC6930866](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6930866)

28. **Phase 1, Open-Label, Dose-Escalation Study to Evaluate Tolerability, Safety, and Immunogenicity of an Intranasal Live Attenuated Respiratory Syncytial Virus Vaccine Expressing Spike Protein of SARS-CoV-2 in Healthy Adults Ages 18 - 69 Years** Meissa Vaccines, Inc. *clinicaltrials.gov* (2021-07-01) <https://clinicaltrials.gov/ct2/show/NCT04798001>

29. **BCG-induced trained immunity: can it offer protection against COVID-19?** Luke AJ O’Neill, Mihai G Netea *Nature Reviews Immunology* (2020-05-11) <https://doi.org/ggvzp3> DOI: [10.1038/s41577-020-0337-y](https://doi.org/10.1038/s41577-020-0337-y) · PMID: [32393823](https://www.ncbi.nlm.nih.gov/pubmed/32393823) · PMCID: [PMC7212510](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7212510)

30. **Efficacy of BCG Vaccination Against Respiratory Tract Infections in Older Adults During the Coronavirus Disease 2019 Pandemic** Simone JCFM Moorlag, Esther Taks, Thijs ten Doesschate, Thomas W van der Vaart, Axel B Janssen, Lisa Müller, Philipp Ostermann, Helga Dijkstra, Heidi Lemmers, Elles Simonetti, … Mihai G Netea *Clinical Infectious Diseases* (2022-03-05) <https://doi.org/gptcjh> DOI: [10.1093/cid/ciac182](https://doi.org/10.1093/cid/ciac182) · PMID: [35247264](https://www.ncbi.nlm.nih.gov/pubmed/35247264) · PMCID: [PMC8903481](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8903481)

31. **BCG Vaccination to Protect Healthcare Workers Against COVID-19 - Full Text View - ClinicalTrials.gov** <https://clinicaltrials.gov/ct2/show/NCT04327206>

32. **BCG Vaccine for Health Care Workers as Defense Against COVID 19 - Full Text View - ClinicalTrials.gov** <https://clinicaltrials.gov/ct2/show/NCT04348370>

33. **Replicating and non-replicating viral vectors for vaccine development** Marjorie Robert-Guroff *Current Opinion in Biotechnology* (2007-12) <https://doi.org/dgfz6w> DOI: [10.1016/j.copbio.2007.10.010](https://doi.org/10.1016/j.copbio.2007.10.010) · PMID: [18063357](https://www.ncbi.nlm.nih.gov/pubmed/18063357) · PMCID: [PMC2245896](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2245896)

34. **Vaccine Types** Office of Infectious Disease and HIV/AIDS Policy (OIDP) *HHS.gov* (2021-04-26) <https://www.hhs.gov/immunization/basics/types/index.html>

35. **Updated vaccine protects from infection with SARS-CoV-2 variants, prevents transmission and is immunogenic against Omicron in hamsters** Sapna Sharma, Thomas Vercruysse, Lorena Sanchez-Felipe, Winnie Kerstens, Madina Rasulova, Rana Abdelnabi, Caroline S Foo, Viktor Lemmens, Dominique Van Looveren, Piet Maes, … Kai Dallmeier *Cold Spring Harbor Laboratory* (2021-11-15) <https://doi.org/gp5bjc> DOI: [10.1101/2021.11.12.468374](https://doi.org/10.1101/2021.11.12.468374)

36. **Vero cell technology for rapid development of inactivated whole virus vaccines for emerging viral diseases** PNoel Barrett, Sara J Terpening, Doris Snow, Ronald R Cobb, Otfried Kistner *Expert Review of Vaccines* (2017-07-27) <https://doi.org/ggt7vf> DOI: [10.1080/14760584.2017.1357471](https://doi.org/10.1080/14760584.2017.1357471) · PMID: [28724343](https://www.ncbi.nlm.nih.gov/pubmed/28724343)

37. **Vaccine delivery: a matter of size, geometry, kinetics and molecular patterns** Martin F Bachmann, Gary T Jennings *Nature Reviews Immunology* (2010-10-15) <https://doi.org/fg5dx9> DOI: [10.1038/nri2868](https://doi.org/10.1038/nri2868) · PMID: [20948547](https://www.ncbi.nlm.nih.gov/pubmed/20948547)

38. **Animal models and vaccines for SARS-CoV infection** Anjeanette Roberts, Elaine W Lamirande, Leatrice Vogel, Jadon P Jackson, Christopher D Paddock, Jeannette Guarner, Sherif R Zaki, Timothy Sheahan, Ralph Baric, Kanta Subbarao *Virus Research* (2008-04) <https://doi.org/brrg6k> DOI: [10.1016/j.virusres.2007.03.025](https://doi.org/10.1016/j.virusres.2007.03.025) · PMID: [17499378](https://www.ncbi.nlm.nih.gov/pubmed/17499378) · PMCID: [PMC2323511](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2323511)

39. **Functional analysis of influenza-specific helper T cell clones in vivo. T cells specific for internal viral proteins provide cognate help for B cell responses to hemagglutinin.** PA Scherle, W Gerhard *Journal of Experimental Medicine* (1986-10-01) <https://doi.org/bp47qh> DOI: [10.1084/jem.164.4.1114](https://doi.org/10.1084/jem.164.4.1114) · PMID: [2944982](https://www.ncbi.nlm.nih.gov/pubmed/2944982) · PMCID: [PMC2188433](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2188433)

40. **Severe acute respiratory syndrome (SARS) coronavirus: application of monoclonal antibodies and development of an effective vaccine** Yasuko Tsunetsugu-Yokota, Kazuo Ohnishi, Toshitada Takemori *Reviews in Medical Virology* (2006) <https://doi.org/dskzwh> DOI: [10.1002/rmv.492](https://doi.org/10.1002/rmv.492) · PMID: [16518829](https://www.ncbi.nlm.nih.gov/pubmed/16518829) · PMCID: [PMC7169118](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7169118)

41. **A subcutaneously injected UV-inactivated SARS coronavirus vaccine elicits systemic humoral immunity in mice** N Takasuka *International Immunology* (2004-08-31) <https://doi.org/bkd6xq> DOI: [10.1093/intimm/dxh143](https://doi.org/10.1093/intimm/dxh143) · PMID: [15314040](https://www.ncbi.nlm.nih.gov/pubmed/15314040) · PMCID: [PMC7108621](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7108621)

42. **Learning from the past: development of safe and effective COVID-19 vaccines** Shan Su, Lanying Du, Shibo Jiang *Nature Reviews Microbiology* (2020-10-16) <https://doi.org/ghmtgp> DOI: [10.1038/s41579-020-00462-y](https://doi.org/10.1038/s41579-020-00462-y) · PMID: [33067570](https://www.ncbi.nlm.nih.gov/pubmed/33067570) · PMCID: [PMC7566580](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7566580)

43. **Immunodominant SARS Coronavirus Epitopes in Humans Elicited both Enhancing and Neutralizing Effects on Infection in Non-human Primates** Qidi Wang, Lianfeng Zhang, Kazuhiko Kuwahara, Li Li, Zijie Liu, Taisheng Li, Hua Zhu, Jiangning Liu, Yanfeng Xu, Jing Xie, … Gang Liu *ACS Infectious Diseases* (2016-03-30) <https://doi.org/ggrcdk> DOI: [10.1021/acsinfecdis.6b00006](https://doi.org/10.1021/acsinfecdis.6b00006) · PMID: [27627203](https://www.ncbi.nlm.nih.gov/pubmed/27627203) · PMCID: [PMC7075522](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7075522)

44. **Immunization with inactivated Middle East Respiratory Syndrome coronavirus vaccine leads to lung immunopathology on challenge with live virus** Anurodh Shankar Agrawal, Xinrong Tao, Abdullah Algaissi, Tania Garron, Krishna Narayanan, Bi-Hung Peng, Robert B Couch, Chien-Te K Tseng *Human Vaccines & Immunotherapeutics* (2016-06-07) <https://doi.org/gmkb76> DOI: [10.1080/21645515.2016.1177688](https://doi.org/10.1080/21645515.2016.1177688) · PMID: [27269431](https://www.ncbi.nlm.nih.gov/pubmed/27269431) · PMCID: [PMC5027702](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5027702)

45. **Single-Dose, Intranasal Immunization with Recombinant Parainfluenza Virus 5 Expressing Middle East Respiratory Syndrome Coronavirus (MERS-CoV) Spike Protein Protects Mice from Fatal MERS-CoV Infection** Kun Li, Zhuo Li, Christine Wohlford-Lenane, David K Meyerholz, Rudragouda Channappanavar, Dong An, Stanley Perlman, Paul B McCray Jr., Biao He *mBio* (2020-04-28) <https://doi.org/ggrzk2> DOI: [10.1128/mbio.00554-20](https://doi.org/10.1128/mbio.00554-20) · PMID: [32265331](https://www.ncbi.nlm.nih.gov/pubmed/32265331) · PMCID: [PMC7157776](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7157776)

46. **Types of Vaccines – COVID19 Vaccine Tracker** <https://covid19.trackvaccines.org/types-of-vaccines/>

47. **Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy adults aged 60 years and older: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial** Zhiwei Wu, Yaling Hu, Miao Xu, Zhen Chen, Wanqi Yang, Zhiwei Jiang, Minjie Li, Hui Jin, Guoliang Cui, Panpan Chen, … Weidong Yin *The Lancet Infectious Diseases* (2021-06) <https://doi.org/fx8z> DOI: [10.1016/s1473-3099(20)30987-7](https://doi.org/10.1016/s1473-3099(20)30987-7) · PMID: [33548194](https://www.ncbi.nlm.nih.gov/pubmed/33548194) · PMCID: [PMC7906628](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7906628)

48. **Development of an inactivated vaccine candidate for SARS-CoV-2** Qiang Gao, Linlin Bao, Haiyan Mao, Lin Wang, Kangwei Xu, Minnan Yang, Yajing Li, Ling Zhu, Nan Wang, Zhe Lv, … Chuan Qin *Science* (2020-07-03) <https://doi.org/ggvckc> DOI: [10.1126/science.abc1932](https://doi.org/10.1126/science.abc1932) · PMID: [32376603](https://www.ncbi.nlm.nih.gov/pubmed/32376603) · PMCID: [PMC7202686](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7202686)

49. **Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial** Yanjun Zhang, Gang Zeng, Hongxing Pan, Changgui Li, Yaling Hu, Kai Chu, Weixiao Han, Zhen Chen, Rong Tang, Weidong Yin, … Fengcai Zhu *The Lancet Infectious Diseases* (2021-02) <https://doi.org/fpcx> DOI: [10.1016/s1473-3099(20)30843-4](https://doi.org/10.1016/s1473-3099(20)30843-4) · PMID: [33217362](https://www.ncbi.nlm.nih.gov/pubmed/33217362) · PMCID: [PMC7832443](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7832443)

50. **Background document on the inactivated vaccine Sinovac-CoronaVac against COVID-19** <https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-vaccines-SAGE_recommendation-Sinovac-CoronaVac-background-2021.1>

51. **Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey** Mine Durusu Tanriover, Hamdi Levent Doğanay, Murat Akova, Hatice Rahmet Güner, Alpay Azap, Sıla Akhan, Şükran Köse, Fatma Şebnem Erdinç, Emin Halis Akalın, Ömer Fehmi Tabak, … Kurtuluş Aksu *The Lancet* (2021-07) <https://doi.org/gk898z> DOI: [10.1016/s0140-6736(21)01429-x](https://doi.org/10.1016/s0140-6736(21)01429-x) · PMID: [34246358](https://www.ncbi.nlm.nih.gov/pubmed/34246358) · PMCID: [PMC8266301](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8266301)

52. **Interim report: Safety and immunogenicity of an inactivated vaccine against SARS-CoV-2 in healthy chilean adults in a phase 3 clinical trial** Susan M Bueno, Katia Abarca, Pablo A González, Nicolás MS Gálvez, Jorge A Soto, Luisa F Duarte, Bárbara M Schultz, Gaspar A Pacheco, Liliana A González, Yaneisi Vázquez, … Alexis M Kalergis *Cold Spring Harbor Laboratory* (2021-04-01) <https://doi.org/gmwn42> DOI: [10.1101/2021.03.31.21254494](https://doi.org/10.1101/2021.03.31.21254494)

53. **Coronavirus Vaccine Tracker** Carl Zimmer, Jonathan Corum, Sui-Lee Wee, Matthew Kristoffersen *The New York Times* (2020-06-10) <https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html>

54. **SARS-CoV-2 vaccines strategies: a comprehensive review of phase 3 candidates** Nikolaos C Kyriakidis, Andrés López-Cortés, Eduardo Vásconez González, Alejandra Barreto Grimaldos, Esteban Ortiz Prado *npj Vaccines* (2021-02-22) <https://doi.org/gjsgc4> DOI: [10.1038/s41541-021-00292-w](https://doi.org/10.1038/s41541-021-00292-w) · PMID: [33619260](https://www.ncbi.nlm.nih.gov/pubmed/33619260) · PMCID: [PMC7900244](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7900244)

55. **Development of an Inactivated Vaccine Candidate, BBIBP-CorV, with Potent Protection against SARS-CoV-2** Hui Wang, Yuntao Zhang, Baoying Huang, Wei Deng, Yaru Quan, Wenling Wang, Wenbo Xu, Yuxiu Zhao, Na Li, Jin Zhang, … Xiaoming Yang *Cell* (2020-08) <https://doi.org/ghms9s> DOI: [10.1016/j.cell.2020.06.008](https://doi.org/10.1016/j.cell.2020.06.008) · PMID: [32778225](https://www.ncbi.nlm.nih.gov/pubmed/32778225) · PMCID: [PMC7275151](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7275151)

56. **Effect of an Inactivated Vaccine Against SARS-CoV-2 on Safety and Immunogenicity Outcomes** Shengli Xia, Kai Duan, Yuntao Zhang, Dongyang Zhao, Huajun Zhang, Zhiqiang Xie, Xinguo Li, Cheng Peng, Yanbo Zhang, Wei Zhang, … Xiaoming Yang *JAMA* (2020-09-08) <https://doi.org/gg72mg> DOI: [10.1001/jama.2020.15543](https://doi.org/10.1001/jama.2020.15543) · PMID: [32789505](https://www.ncbi.nlm.nih.gov/pubmed/32789505) · PMCID: [PMC7426884](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7426884)

57. **Coronavirus Pandemic (COVID-19)** Hannah Ritchie, Edouard Mathieu, Lucas Rodés-Guirao, Cameron Appel, Charlie Giattino, Esteban Ortiz-Ospina, Joe Hasell, Bobbie Macdonald, Diana Beltekian, Max Roser *Our World in Data* (2020-03-05) <https://ourworldindata.org/coronavirus>

58. **GitHub - geopandas/geopandas: Python tools for geographic data** GitHub <https://github.com/geopandas/geopandas>

59. **Immunogenicity and protective efficacy of BBV152: a whole virion inactivated SARS CoV-2 vaccine in the Syrian hamster model** Sreelekshmy Mohandas, Pragya D Yadav, Anita Shete, Priya Abraham, Krishna Mohan, Gajanan Sapkal, Chandrashekhar Mote, Dimpal Nyayanit, Nivedita Gupta, VK Srini, … Balram Bhargava *Research Square Platform LLC* (2020-09-16) <https://doi.org/gmwn5d> DOI: [10.21203/rs.3.rs-76768/v1](https://doi.org/10.21203/rs.3.rs-76768/v1)

60. **Immunogenicity and protective efficacy of inactivated SARS-CoV-2 vaccine candidate, BBV152 in rhesus macaques** Pragya D Yadav, Raches Ella, Sanjay Kumar, Dilip R Patil, Sreelekshmy Mohandas, Anita M Shete, Krishna M Vadrevu, Gaurav Bhati, Gajanan Sapkal, Himanshu Kaushal, … Balram Bhargava *Nature Communications* (2021-03-02) <https://doi.org/gmwn4c> DOI: [10.1038/s41467-021-21639-w](https://doi.org/10.1038/s41467-021-21639-w) · PMID: [33654090](https://www.ncbi.nlm.nih.gov/pubmed/33654090) · PMCID: [PMC7925524](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7925524)

61. **Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: a double-blind, randomised, phase 1 trial** Raches Ella, Krishna Mohan Vadrevu, Harsh Jogdand, Sai Prasad, Siddharth Reddy, Vamshi Sarangi, Brunda Ganneru, Gajanan Sapkal, Pragya Yadav, Priya Abraham, … Balram Bhargava *The Lancet Infectious Diseases* (2021-05) <https://doi.org/gkrthh> DOI: [10.1016/s1473-3099(20)30942-7](https://doi.org/10.1016/s1473-3099(20)30942-7) · PMID: [33485468](https://www.ncbi.nlm.nih.gov/pubmed/33485468) · PMCID: [PMC7825810](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7825810)

62. **Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: interim results from a double-blind, randomised, multicentre, phase 2 trial, and 3-month follow-up of a double-blind, randomised phase 1 trial** Raches Ella, Siddharth Reddy, Harsh Jogdand, Vamshi Sarangi, Brunda Ganneru, Sai Prasad, Dipankar Das, Dugyala Raju, Usha Praturi, Gajanan Sapkal, … Krishna Mohan Vadrevu *The Lancet Infectious Diseases* (2021-07) <https://doi.org/gh7597> DOI: [10.1016/s1473-3099(21)00070-0](https://doi.org/10.1016/s1473-3099(21)00070-0) · PMID: [33705727](https://www.ncbi.nlm.nih.gov/pubmed/33705727) · PMCID: [PMC8221739](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8221739)

63. **Bharat Biotech: Covaxin – COVID19 Vaccine Tracker** <https://covid19.trackvaccines.org/vaccines/9/>

64. **Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial** Shengli Xia, Yuntao Zhang, Yanxia Wang, Hui Wang, Yunkai Yang, George Fu Gao, Wenjie Tan, Guizhen Wu, Miao Xu, Zhiyong Lou, … Xiaoming Yang *The Lancet Infectious Diseases* (2021-01) <https://doi.org/ghjkrf> DOI: [10.1016/s1473-3099(20)30831-8](https://doi.org/10.1016/s1473-3099(20)30831-8) · PMID: [33069281](https://www.ncbi.nlm.nih.gov/pubmed/33069281) · PMCID: [PMC7561304](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7561304)

65. **How the Sinovac Vaccine Works** Jonathan Corum, Carl Zimmer *The New York Times* (2020-12-24) <https://www.nytimes.com/interactive/2020/health/sinovac-covid-19-vaccine.html>

66. **Officials Stress That the Pandemic ‘Is Not Over Yet’ as U.S. Vaccinations Begin** Karen Zraick *The New York Times* (2020-12-16) <https://www.nytimes.com/live/2020/12/16/world/covid-19-coronavirus>

67. **Ensayo Clínico de Fase III, Aleatorio, Doble Ciego y Controlado Con Placebo Paralelo, Para Evaluar la Seguridad y la Eficacia Protectora de la Vacuna Inactivada Contra el SARS-CoV-2 en la Población Sana de 18 años o más, en Perú** Universidad Peruana Cayetano Heredia *clinicaltrials.gov* (2021-04-27) <https://clinicaltrials.gov/ct2/show/NCT04612972>

68. **Effect of 2 Inactivated SARS-CoV-2 Vaccines on Symptomatic COVID-19 Infection in Adults** Nawal Al Kaabi, Yuntao Zhang, Shengli Xia, Yunkai Yang, Manaf M Al Qahtani, Najiba Abdulrazzaq, Majed Al Nusair, Mohamed Hassany, Jaleela S Jawad, Jehad Abdalla, … Xiaoming Yang *JAMA* (2021-05-26) <https://doi.org/gj7khd> DOI: [10.1001/jama.2021.8565](https://doi.org/10.1001/jama.2021.8565) · PMID: [34037666](https://www.ncbi.nlm.nih.gov/pubmed/34037666) · PMCID: [PMC8156175](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8156175)

69. **Efficacy, safety, and lot to lot immunogenicity of an inactivated SARS-CoV-2 vaccine (BBV152): a, double-blind, randomised, controlled phase 3 trial** Raches Ella, Siddarth Reddy, William Blackwelder, Varsha Potdar, Pragya Yadav, Vamshi Sarangi, Vinay Kumar Aileni, Suman Kanungo, Sanjay Rai, Prabhakar Reddy, … *Cold Spring Harbor Laboratory* (2021-07-02) <https://doi.org/gmns9m> DOI: [10.1101/2021.06.30.21259439](https://doi.org/10.1101/2021.06.30.21259439)

70. **Sinopharm's COVID-19 vaccine 79% effective, seeks approval in China** Reuters (2020-12-30) <https://www.reuters.com/article/health-coronavirus-china-vaccine-int-idUSKBN2940CA>

71. **Brazil institute says CoronaVac efficacy above 50%, but delays full results** Reuters (2020-12-23) <https://www.reuters.com/article/us-health-coronavirus-sinovac-brazil-idUSKBN28X2CR>

72. **Turkey and Brazil Say Chinese Vaccine Effective, With Sparse Supporting Data** Carl Zimmer, Ernesto Londoño *The New York Times* (2020-12-25) <https://www.nytimes.com/2020/12/25/health/turkey-brazil-sinovac-coronavirus-vaccine.html>

73. **Effectiveness of an Inactivated SARS-CoV-2 Vaccine in Chile** Alejandro Jara, Eduardo A Undurraga, Cecilia González, Fabio Paredes, Tomás Fontecilla, Gonzalo Jara, Alejandra Pizarro, Johanna Acevedo, Katherinne Leo, Francisco Leon, … Rafael Araos *New England Journal of Medicine* (2021-09-02) <https://doi.org/gk475w> DOI: [10.1056/nejmoa2107715](https://doi.org/10.1056/nejmoa2107715) · PMID: [34233097](https://www.ncbi.nlm.nih.gov/pubmed/34233097) · PMCID: [PMC8279092](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8279092)

74. **To Boldly Remember Where We Have Already Been** Nathaniel L Moir *Journal of Applied History* (2020-09-28) <https://doi.org/gp4rqf> DOI: [10.1163/25895893-bja10009](https://doi.org/10.1163/25895893-bja10009)

75. **Suspension of supply of COVID-19 vaccine (COVAXIN®)** WHO - Prequalification of Medical Products (IVDs, Medicines, Vaccines and Immunization Devices, Vector Control) (2022-04-01) <https://extranet.who.int/pqweb/vaccines/suspension-supply-covid-19-vaccine-covaxin>

76. **Vaccine-Associated Disease Enhancement (VADE): Considerations in Postvaccination COVID-19** Rahajeng N Tunjungputri, Erpryta Nurdia Tetrasiwi, Merlinda Veronica, Jacub Pandelaki, Fera Ibrahim, Erni Juwita Nelwan *Case Reports in Medicine* (2021-10-29) <https://doi.org/gphtqw> DOI: [10.1155/2021/9673453](https://doi.org/10.1155/2021/9673453) · PMID: [34745267](https://www.ncbi.nlm.nih.gov/pubmed/34745267) · PMCID: [PMC8570879](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8570879)

77. **Susceptibility of Circulating SARS-CoV-2 Variants to Neutralization** Guo-Lin Wang, Zhuang-Ye Wang, Li-Jun Duan, Qing-Chuan Meng, Ming-Dong Jiang, Jing Cao, Lin Yao, Ka-Li Zhu, Wu-Chun Cao, Mai-Juan Ma *New England Journal of Medicine* (2021-06-17) <https://doi.org/gjnrhz> DOI: [10.1056/nejmc2103022](https://doi.org/10.1056/nejmc2103022) · PMID: [33822491](https://www.ncbi.nlm.nih.gov/pubmed/33822491) · PMCID: [PMC8063885](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8063885)

78. **Comparable neutralization of SARS-CoV-2 Delta AY.1 and Delta in individuals sera vaccinated with BBV152** Pragya D Yadav, Rima R Sahay, Gajanan Sapkal, Dimpal Nyayanit, Anita M Shete, Gururaj Deshpande, Deepak Y Patil, Nivedita Gupta, Sanjay Kumar, Priya Abraham, … Balram Bhargava *Cold Spring Harbor Laboratory* (2021-08-01) <https://doi.org/gmx72g> DOI: [10.1101/2021.07.30.454511](https://doi.org/10.1101/2021.07.30.454511)

79. **Neutralization of Beta and Delta variant with sera of COVID-19 recovered cases and vaccinees of inactivated COVID-19 vaccine BBV152/Covaxin** Pragya D Yadav, Gajanan N Sapkal, Raches Ella, Rima R Sahay, Dimpal A Nyayanit, Deepak Y Patil, Gururaj Deshpande, Anita M Shete, Nivedita Gupta, VKrishna Mohan, … Balram Bhargava *Journal of Travel Medicine* (2021-07-06) <https://doi.org/gmwn4x> DOI: [10.1093/jtm/taab104](https://doi.org/10.1093/jtm/taab104) · PMID: [34230972](https://www.ncbi.nlm.nih.gov/pubmed/34230972) · PMCID: [PMC8344909](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8344909)

80. **Inactivated COVID-19 vaccine BBV152/COVAXIN effectively neutralizes recently emerged B.1.1.7 variant of SARS-CoV-2** Gajanan N Sapkal, Pragya D Yadav, Raches Ella, Gururaj R Deshpande, Rima R Sahay, Nivedita Gupta, Krishna Mohan Vadrevu, Priya Abraham, Samiran Panda, Balram Bhargava *Journal of Travel Medicine* (2021-03-27) <https://doi.org/gjs7m8> DOI: [10.1093/jtm/taab051](https://doi.org/10.1093/jtm/taab051) · PMID: [33772577](https://www.ncbi.nlm.nih.gov/pubmed/33772577) · PMCID: [PMC8083765](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8083765)

81. **Neutralization of SARS-CoV-2 VOC 501Y.V2 by human antisera elicited by both inactivated BBIBP-CorV and recombinant dimeric RBD ZF2001 vaccines** Baoying Huang, Lianpan Dai, Hui Wang, Zhongyu Hu, Xiaoming Yang, Wenjie Tan, George F Gao *Cold Spring Harbor Laboratory* (2021-02-02) <https://doi.org/gh2px7> DOI: [10.1101/2021.02.01.429069](https://doi.org/10.1101/2021.02.01.429069)

82. **Antibody and T cell responses to Sinopharm/BBIBP-CorV in naïve and previously infected individuals in Sri Lanka** Chandima Jeewandara, Inoka Sepali Aberathna, Pradeep Darshana Pushpakumara, Achala Kamaladasa, Dinuka Guruge, Deshni Jayathilaka, Banuri Gunasekara, Shyrar Tanussiya, Heshan Kuruppu, Thushali Ranasinghe, … Gathsaurie Neelika Malavige *Cold Spring Harbor Laboratory* (2021-07-19) <https://doi.org/gk86qx> DOI: [10.1101/2021.07.15.21260621](https://doi.org/10.1101/2021.07.15.21260621)

83. **They Relied on Chinese Vaccines. Now They’re Battling Outbreaks.** Sui-Lee Wee *The New York Times* (2021-06-22) <https://www.nytimes.com/2021/06/22/business/economy/china-vaccines-covid-outbreak.html>

84. **An Open-label,Phase Ⅳ Clinical Trial to Evaluate the Immunogenicity and Safety of the Inactivated SARS-CoV-2 Vaccine (Vero Cell) in Healthy Population Aged From 18 to 59 Years.** Sinovac Research and Development Co., Ltd. *clinicaltrials.gov* (2021-09-22) <https://clinicaltrials.gov/ct2/show/NCT04962308>

85. **Covaxin booster dose: What is it? What does govt say about this?** Hindustan Times (2021-07-07) <https://www.hindustantimes.com/india-news/covaxin-booster-dose-what-is-it-what-does-govt-say-about-this-101625644184446.html>

86. **A booster dose is immunogenic and will be needed for older adults who have completed two doses vaccination with CoronaVac: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial** Minjie Li, Juan Yang, Lin Wang, Qianhui Wu, Zhiwei Wu, Wen Zheng, Lei Wang, Wanying Lu, Xiaowei Deng, Cheng Peng, … Weidong Yin *Cold Spring Harbor Laboratory* (2021-08-08) <https://doi.org/grsh> DOI: [10.1101/2021.08.03.21261544](https://doi.org/10.1101/2021.08.03.21261544)

87. **Immunogenicity and safety of a third dose, and immune persistence of CoronaVac vaccine in healthy adults aged 18-59 years: interim results from a double-blind, randomized, placebo-controlled phase 2 clinical trial** Hongxing Pan, Qianhui Wu, Gang Zeng, Juan Yang, Deyu Jiang, Xiaowei Deng, Kai Chu, Wen Zheng, Fengcai Zhu, Hongjie Yu, Weidong Yin *Cold Spring Harbor Laboratory* (2021-07-25) <https://doi.org/gm2g4h> DOI: [10.1101/2021.07.23.21261026](https://doi.org/10.1101/2021.07.23.21261026)

88. **Robust induction of B cell and T cell responses by a third dose of inactivated SARS-CoV-2 vaccine** Yihao Liu, Qin Zeng, Caiguanxi Deng, Mengyuan Li, Liubing Li, Dayue Liu, Ming Liu, Xinyuan Ruan, Jie Mei, Ruohui Mo, … Haipeng Xiao *Cold Spring Harbor Laboratory* (2021-09-15) <https://doi.org/gmx72k> DOI: [10.1101/2021.09.12.21263373](https://doi.org/10.1101/2021.09.12.21263373)

89. **China approves first mixed-vaccine trial as Delta spreads** <https://medicalxpress.com/news/2021-08-china-mixed-vaccine-trial-delta.html>

90. **Reactogenicidad, Seguridad e Inmunogenicidad de Dosis de Refuerzo de Vacunas Contra SARS-CoV-2 en Chile (Estudio REFUERZO)** Rafael Araos *clinicaltrials.gov* (2021-08-04) <https://clinicaltrials.gov/ct2/show/NCT04992182>

91. **Heterologous prime-boost immunization with CoronaVac and Convidecia** Jingxin Li, Lihua Hou, Xiling Guo, Pengfei Jin, Shipo Wu, Jiahong Zhu, Hongxing Pan, Xue Wang, Zhizhou Song, Jingxuan Wan, … Fengcai Zhu *Cold Spring Harbor Laboratory* (2021-09-06) <https://doi.org/gmx72j> DOI: [10.1101/2021.09.03.21263062](https://doi.org/10.1101/2021.09.03.21263062)

92. **Heterologous AD5-nCOV plus CoronaVac versus homologous CoronaVac vaccination: a randomized phase 4 trial** Jingxin Li, Lihua Hou, Xiling Guo, Pengfei Jin, Shipo Wu, Jiahong Zhu, Hongxing Pan, Xue Wang, Zhizhou Song, Jingxuan Wan, … Fengcai Zhu *Nature Medicine* (2022-01-27) <https://doi.org/gn93qp> DOI: [10.1038/s41591-021-01677-z](https://doi.org/10.1038/s41591-021-01677-z) · PMID: [35087233](https://www.ncbi.nlm.nih.gov/pubmed/35087233) · PMCID: [PMC8863573](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8863573)

93. **Neutralizing antibodies against the SARS-CoV-2 Delta and Omicron variants following heterologous CoronaVac plus BNT162b2 booster vaccination** Eddy Pérez-Then, Carolina Lucas, Valter Silva Monteiro, Marija Miric, Vivian Brache, Leila Cochon, Chantal BF Vogels, Amyn A Malik, Elena De la Cruz, Aidelis Jorge, … Akiko Iwasaki *Nature Medicine* (2022-01-20) <https://doi.org/gn7rts> DOI: [10.1038/s41591-022-01705-6](https://doi.org/10.1038/s41591-022-01705-6) · PMID: [35051990](https://www.ncbi.nlm.nih.gov/pubmed/35051990) · PMCID: [PMC8938264](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8938264)

94. **Reactogenicidad, Seguridad e Inmunogenicidad de Dosis de Refuerzo de Vacunas Contra SARS-CoV-2 en Chile (Estudio REFUERZO)** Rafael Araos *clinicaltrials.gov* (2021-08-04) <https://clinicaltrials.gov/ct2/show/NCT04992182>

95. **Vaccines, new opportunities for a new society** Rino Rappuoli, Mariagrazia Pizza, Giuseppe Del Giudice, Ennio De Gregorio *Proceedings of the National Academy of Sciences* (2014-08-18) <https://doi.org/f6fdps> DOI: [10.1073/pnas.1402981111](https://doi.org/10.1073/pnas.1402981111) · PMID: [25136130](https://www.ncbi.nlm.nih.gov/pubmed/25136130) · PMCID: [PMC4151714](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4151714)

96. **Virus-Like Particles, a Versatile Subunit Vaccine Platform** Braeden Donaldson, Farah Al-Barwani, Vivienne Young, Sarah Scullion, Vernon Ward, Sarah Young *Advances in Delivery Science and Technology* (2014-11-01) <https://doi.org/gptgmx> DOI: [10.1007/978-1-4939-1417-3\_9](https://doi.org/10.1007/978-1-4939-1417-3_9) · PMCID: [PMC7121566](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7121566)

97. **Recombinant protein vaccines, a proven approach against coronavirus pandemics** Jeroen Pollet, Wen-Hsiang Chen, Ulrich Strych *Advanced Drug Delivery Reviews* (2021-03) <https://doi.org/gh7wss> DOI: [10.1016/j.addr.2021.01.001](https://doi.org/10.1016/j.addr.2021.01.001) · PMID: [33421475](https://www.ncbi.nlm.nih.gov/pubmed/33421475) · PMCID: [PMC7788321](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7788321)

98. **Virus-like particles: preparation, immunogenicity and their roles as nanovaccines and drug nanocarriers** Saghi Nooraei, Howra Bahrulolum, Zakieh Sadat Hoseini, Camellia Katalani, Abbas Hajizade, Andrew J Easton, Gholamreza Ahmadian *Journal of Nanobiotechnology* (2021-02-25) <https://doi.org/gk635z> DOI: [10.1186/s12951-021-00806-7](https://doi.org/10.1186/s12951-021-00806-7) · PMID: [33632278](https://www.ncbi.nlm.nih.gov/pubmed/33632278) · PMCID: [PMC7905985](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7905985)

99. **Vaccine Design** Michael F Powell, Mark J Newman (editors) *Pharmaceutical Biotechnology* (1995) <https://doi.org/gh3zp9> DOI: [10.1007/978-1-4615-1823-5](https://doi.org/10.1007/978-1-4615-1823-5)

100. **Virus-like particles as immunogens** Rob Noad, Polly Roy *Trends in Microbiology* (2003-09) <https://doi.org/dg35hw> DOI: [10.1016/s0966-842x(03)00208-7](https://doi.org/10.1016/s0966-842x(03)00208-7)

101. **Peptide Vaccine: Progress and Challenges** Weidang Li, Medha Joshi, Smita Singhania, Kyle Ramsey, Ashlesh Murthy *Vaccines* (2014-07-02) <https://doi.org/gcfszb> DOI: [10.3390/vaccines2030515](https://doi.org/10.3390/vaccines2030515) · PMID: [26344743](https://www.ncbi.nlm.nih.gov/pubmed/26344743) · PMCID: [PMC4494216](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4494216)

102. **Role of AS04 in human papillomavirus vaccine: mode of action and clinical profile** Nathalie Garçon, Martine Wettendorff, Marcelle Van Mechelen *Expert Opinion on Biological Therapy* (2011-04-04) <https://doi.org/bvtmpk> DOI: [10.1517/14712598.2011.573624](https://doi.org/10.1517/14712598.2011.573624) · PMID: [21457083](https://www.ncbi.nlm.nih.gov/pubmed/21457083)

103. **Vaccine adjuvants: Understanding the structure and mechanism of adjuvanticity** Shuting Shi, Haoru Zhu, Xinyu Xia, Zhihui Liang, Xuehu Ma, Bingbing Sun *Vaccine* (2019-05) <https://doi.org/gk6vqb> DOI: [10.1016/j.vaccine.2019.04.055](https://doi.org/10.1016/j.vaccine.2019.04.055) · PMID: [31047671](https://www.ncbi.nlm.nih.gov/pubmed/31047671)

104. **Immunogenicity of a receptor-binding domain of SARS coronavirus spike protein in mice: Implications for a subunit vaccine** Alexander N Zakhartchouk, Chetna Sharon, Malathy Satkunarajah, Thierry Auperin, Sathiyanarayanan Viswanathan, George Mutwiri, Martin Petric, Raymond H See, Robert C Brunham, BBrett Finlay, … Lorne A Babiuk *Vaccine* (2007-01) <https://doi.org/b92cpk> DOI: [10.1016/j.vaccine.2006.06.084](https://doi.org/10.1016/j.vaccine.2006.06.084) · PMID: [16919855](https://www.ncbi.nlm.nih.gov/pubmed/16919855) · PMCID: [PMC7115608](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7115608)

105. **Receptor-binding domain of SARS-CoV spike protein induces long-term protective immunity in an animal model** Lanying Du, Guangyu Zhao, Yuxian He, Yan Guo, Bo-Jian Zheng, Shibo Jiang, Yusen Zhou *Vaccine* (2007-04) <https://doi.org/drpspr> DOI: [10.1016/j.vaccine.2006.10.031](https://doi.org/10.1016/j.vaccine.2006.10.031) · PMID: [17092615](https://www.ncbi.nlm.nih.gov/pubmed/17092615) · PMCID: [PMC7115660](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7115660)

106. **A 219-mer CHO-Expressing Receptor-Binding Domain of SARS-CoV S Protein Induces Potent Immune Responses and Protective Immunity** Lanying Du, Guangyu Zhao, Chris CS Chan, Lin Li, Yuxian He, Yusen Zhou, Bo-Jian Zheng, Shibo Jiang *Viral Immunology* (2010-04) <https://doi.org/b5ghkz> DOI: [10.1089/vim.2009.0090](https://doi.org/10.1089/vim.2009.0090) · PMID: [20374001](https://www.ncbi.nlm.nih.gov/pubmed/20374001) · PMCID: [PMC2883479](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2883479)

107. **Antigenic and Immunogenic Characterization of Recombinant Baculovirus-Expressed Severe Acute Respiratory Syndrome Coronavirus Spike Protein: Implication for Vaccine Design** Yuxian He, Jingjing Li, Susanne Heck, Sara Lustigman, Shibo Jiang *Journal of Virology* (2006-06-15) <https://doi.org/bkcf55> DOI: [10.1128/jvi.00083-06](https://doi.org/10.1128/jvi.00083-06) · PMID: [16731915](https://www.ncbi.nlm.nih.gov/pubmed/16731915) · PMCID: [PMC1472569](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1472569)

108. **Immunogenicity and Protection Efficacy of Monomeric and Trimeric Recombinant SARS Coronavirus Spike Protein Subunit Vaccine Candidates** Jie Li, Laura Ulitzky, Erica Silberstein, Deborah R Taylor, Raphael Viscidi *Viral Immunology* (2013-04) <https://doi.org/f4tdd4> DOI: [10.1089/vim.2012.0076](https://doi.org/10.1089/vim.2012.0076) · PMID: [23573979](https://www.ncbi.nlm.nih.gov/pubmed/23573979) · PMCID: [PMC3624630](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3624630)

109. **Antigenicity and immunogenicity of SARS-CoV S protein receptor-binding domain stably expressed in CHO cells** Lanying Du, Guangyu Zhao, Lin Li, Yuxian He, Yusen Zhou, Bo-Jian Zheng, Shibo Jiang *Biochemical and Biophysical Research Communications* (2009-07) <https://doi.org/brx5bg> DOI: [10.1016/j.bbrc.2009.05.003](https://doi.org/10.1016/j.bbrc.2009.05.003) · PMID: [19422787](https://www.ncbi.nlm.nih.gov/pubmed/19422787) · PMCID: [PMC2750803](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2750803)

110. **Elicitation of Immunity in Mice After Immunization with the S2 Subunit of the Severe Acute Respiratory Syndrome Coronavirus** Yingjun Guo, Shuhan Sun, Kaiyu Wang, Shu Zhang, Weijia Zhu, Ze Chen *DNA and Cell Biology* (2005-08) <https://doi.org/bqrpd7> DOI: [10.1089/dna.2005.24.510](https://doi.org/10.1089/dna.2005.24.510) · PMID: [16101349](https://www.ncbi.nlm.nih.gov/pubmed/16101349)

111. **Identification of Immunodominant Epitopes on the Membrane Protein of the Severe Acute Respiratory Syndrome-Associated Coronavirus** Yuxian He, Yusen Zhou, Pamela Siddiqui, Jinkui Niu, Shibo Jiang *Journal of Clinical Microbiology* (2005-08) <https://doi.org/bn4tfg> DOI: [10.1128/jcm.43.8.3718-3726.2005](https://doi.org/10.1128/jcm.43.8.3718-3726.2005) · PMID: [16081901](https://www.ncbi.nlm.nih.gov/pubmed/16081901) · PMCID: [PMC1234014](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1234014)

112. **Boosted expression of the SARS-CoV nucleocapsid protein in tobacco and its immunogenicity in mice** Nuoyan Zheng, Ran Xia, Cuiping Yang, Bojiao Yin, Yin Li, Chengguo Duan, Liming Liang, Huishan Guo, Qi Xie *Vaccine* (2009-08) <https://doi.org/cmwbzj> DOI: [10.1016/j.vaccine.2009.05.073](https://doi.org/10.1016/j.vaccine.2009.05.073) · PMID: [19523911](https://www.ncbi.nlm.nih.gov/pubmed/19523911) · PMCID: [PMC7115566](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7115566)

113. **Immunological characterizations of the nucleocapsid protein based SARS vaccine candidates** S LIU, C LENG, S LIEN, H CHI, C HUANG, C LIN, W LIAN, C CHEN, S HSIEH, P CHONG *Vaccine* (2006-04-12) <https://doi.org/crmzqd> DOI: [10.1016/j.vaccine.2006.01.058](https://doi.org/10.1016/j.vaccine.2006.01.058) · PMID: [16494977](https://www.ncbi.nlm.nih.gov/pubmed/16494977) · PMCID: [PMC7115648](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7115648)

114. **Subunit Vaccines Against Emerging Pathogenic Human Coronaviruses** Ning Wang, Jian Shang, Shibo Jiang, Lanying Du *Frontiers in Microbiology* (2020-02-28) <https://doi.org/ggpxnq> DOI: [10.3389/fmicb.2020.00298](https://doi.org/10.3389/fmicb.2020.00298) · PMID: [32265848](https://www.ncbi.nlm.nih.gov/pubmed/32265848) · PMCID: [PMC7105881](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7105881)

115. **Yeast-expressed recombinant protein of the receptor-binding domain in SARS-CoV spike protein with deglycosylated forms as a SARS vaccine candidate** Wen-Hsiang Chen, Lanying Du, Shivali M Chag, Cuiqing Ma, Nancy Tricoche, Xinrong Tao, Christopher A Seid, Elissa M Hudspeth, Sara Lustigman, Chien-Te K Tseng, … Shibo Jiang *Human Vaccines & Immunotherapeutics* (2013-12-30) <https://doi.org/ghms54> DOI: [10.4161/hv.27464](https://doi.org/10.4161/hv.27464) · PMID: [24355931](https://www.ncbi.nlm.nih.gov/pubmed/24355931) · PMCID: [PMC4130269](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4130269)

116. **Evaluation of candidate vaccine approaches for MERS-CoV** Lingshu Wang, Wei Shi, MGordon Joyce, Kayvon Modjarrad, Yi Zhang, Kwanyee Leung, Christopher R Lees, Tongqing Zhou, Hadi M Yassine, Masaru Kanekiyo, … Barney S Graham *Nature Communications* (2015-07-28) <https://doi.org/f7mqhd> DOI: [10.1038/ncomms8712](https://doi.org/10.1038/ncomms8712) · PMID: [26218507](https://www.ncbi.nlm.nih.gov/pubmed/26218507) · PMCID: [PMC4525294](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4525294)

117. **MERS-CoV spike protein: Targets for vaccines and therapeutics** Qihui Wang, Gary Wong, Guangwen Lu, Jinghua Yan, George F Gao *Antiviral Research* (2016-09) <https://doi.org/f86fvj> DOI: [10.1016/j.antiviral.2016.07.015](https://doi.org/10.1016/j.antiviral.2016.07.015) · PMID: [27468951](https://www.ncbi.nlm.nih.gov/pubmed/27468951) · PMCID: [PMC7113765](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7113765)

118. **Recombinant Receptor Binding Domain Protein Induces Partial Protective Immunity in Rhesus Macaques Against Middle East Respiratory Syndrome Coronavirus Challenge** Jiaming Lan, Yanfeng Yao, Yao Deng, Hong Chen, Guangwen Lu, Wen Wang, Linlin Bao, Wei Deng, Qiang Wei, George F Gao, … Wenjie Tan *EBioMedicine* (2015-10) <https://doi.org/gfn5b7> DOI: [10.1016/j.ebiom.2015.08.031](https://doi.org/10.1016/j.ebiom.2015.08.031) · PMID: [26629538](https://www.ncbi.nlm.nih.gov/pubmed/26629538) · PMCID: [PMC4634622](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4634622)

119. **Tailoring Subunit Vaccine Immunity with Adjuvant Combinations and Delivery Routes Using the Middle East Respiratory Coronavirus (MERS-CoV) Receptor-Binding Domain as an Antigen** Jiaming Lan, Yao Deng, Hong Chen, Guangwen Lu, Wen Wang, Xiaojuan Guo, Zhuozhuang Lu, George F Gao, Wenjie Tan *PLoS ONE* (2014-11-18) <https://doi.org/gh4zb6> DOI: [10.1371/journal.pone.0112602](https://doi.org/10.1371/journal.pone.0112602) · PMID: [25405618](https://www.ncbi.nlm.nih.gov/pubmed/25405618) · PMCID: [PMC4236105](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4236105)

120. **Engineering a stable CHO cell line for the expression of a MERS-coronavirus vaccine antigen** Mun Peak Nyon, Lanying Du, Chien-Te Kent Tseng, Christopher A Seid, Jeroen Pollet, Kevin S Naceanceno, Anurodh Agrawal, Abdullah Algaissi, Bi-Hung Peng, Wanbo Tai, … Peter J Hotez *Vaccine* (2018-03) <https://doi.org/gdd62m> DOI: [10.1016/j.vaccine.2018.02.065](https://doi.org/10.1016/j.vaccine.2018.02.065) · PMID: [29496347](https://www.ncbi.nlm.nih.gov/pubmed/29496347) · PMCID: [PMC5860679](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5860679)

121. **A recombinant receptor-binding domain of MERS-CoV in trimeric form protects human dipeptidyl peptidase 4 (hDPP4) transgenic mice from MERS-CoV infection** Wanbo Tai, Guangyu Zhao, Shihun Sun, Yan Guo, Yufei Wang, Xinrong Tao, Chien-Te K Tseng, Fang Li, Shibo Jiang, Lanying Du, Yusen Zhou *Virology* (2016-12) <https://doi.org/f9c5sn> DOI: [10.1016/j.virol.2016.10.005](https://doi.org/10.1016/j.virol.2016.10.005) · PMID: [27750111](https://www.ncbi.nlm.nih.gov/pubmed/27750111) · PMCID: [PMC5167628](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5167628)

122. **Immunogenicity and structures of a rationally designed prefusion MERS-CoV spike antigen** Jesper Pallesen, Nianshuang Wang, Kizzmekia S Corbett, Daniel Wrapp, Robert N Kirchdoerfer, Hannah L Turner, Christopher A Cottrell, Michelle M Becker, Lingshu Wang, Wei Shi, … Jason S McLellan *Proceedings of the National Academy of Sciences* (2017-08-14) <https://doi.org/gbwk7p> DOI: [10.1073/pnas.1707304114](https://doi.org/10.1073/pnas.1707304114) · PMID: [28807998](https://www.ncbi.nlm.nih.gov/pubmed/28807998) · PMCID: [PMC5584442](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5584442)

123. **The Amino Acids 736–761 of the MERS-CoV Spike Protein Induce Neutralizing Antibodies: Implications for the Development of Vaccines and Antiviral Agents** Yang Yang, Yao Deng, Bo Wen, Huijuan Wang, Xin Meng, Jiaming Lan, George F Gao, Wenjie Tan *Viral Immunology* (2014-12) <https://doi.org/f6rjbb> DOI: [10.1089/vim.2014.0080](https://doi.org/10.1089/vim.2014.0080) · PMID: [25387086](https://www.ncbi.nlm.nih.gov/pubmed/25387086) · PMCID: [PMC4259179](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4259179)

124. **The recombinant N-terminal domain of spike proteins is a potential vaccine against Middle East respiratory syndrome coronavirus (MERS-CoV) infection** Lan Jiaming, Yao Yanfeng, Deng Yao, Hu Yawei, Bao Linlin, Huang Baoying, Yan Jinghua, George F Gao, Qin Chuan, Tan Wenjie *Vaccine* (2017-01) <https://doi.org/f9htwb> DOI: [10.1016/j.vaccine.2016.11.064](https://doi.org/10.1016/j.vaccine.2016.11.064) · PMID: [27899228](https://www.ncbi.nlm.nih.gov/pubmed/27899228) · PMCID: [PMC7115548](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7115548)

125. **Vaccines based on virus-like nano-particles for use against Middle East Respiratory Syndrome (MERS) coronavirus** Alireza Hashemzadeh, Amir Avan, Gordon A Ferns, Majid Khazaei *Vaccine* (2020-08) <https://doi.org/gg4rkj> DOI: [10.1016/j.vaccine.2020.07.003](https://doi.org/10.1016/j.vaccine.2020.07.003) · PMID: [32684497](https://www.ncbi.nlm.nih.gov/pubmed/32684497) · PMCID: [PMC7837099](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7837099)

126. **Purified coronavirus spike protein nanoparticles induce coronavirus neutralizing antibodies in mice** Christopher M Coleman, Ye V Liu, Haiyan Mu, Justin K Taylor, Michael Massare, David C Flyer, Gregory M Glenn, Gale E Smith, Matthew B Frieman *Vaccine* (2014-05) <https://doi.org/f2rn4w> DOI: [10.1016/j.vaccine.2014.04.016](https://doi.org/10.1016/j.vaccine.2014.04.016) · PMID: [24736006](https://www.ncbi.nlm.nih.gov/pubmed/24736006) · PMCID: [PMC4058772](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4058772)

127. **MERS-CoV virus-like particles produced in insect cells induce specific humoural and cellular imminity in rhesus macaques** Chong Wang, Xuexing Zheng, Weiwei Gai, Yongkun Zhao, Hualei Wang, Haijun Wang, Na Feng, Hang Chi, Boning Qiu, Nan Li, … Xianzhu Xia *Oncotarget* (2016-03-30) <https://doi.org/f92z2j> DOI: [10.18632/oncotarget.8475](https://doi.org/10.18632/oncotarget.8475) · PMID: [27050368](https://www.ncbi.nlm.nih.gov/pubmed/27050368) · PMCID: [PMC5355045](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5355045)

128. **Significant Spike-Specific IgG and Neutralizing Antibodies in Mice Induced by a Novel Chimeric Virus-Like Particle Vaccine Candidate for Middle East Respiratory Syndrome Coronavirus** Jiaming Lan, Yao Deng, Jingdong Song, Baoying Huang, Wenling Wang, Wenjie Tan *Virologica Sinica* (2018-10) <https://doi.org/gpmnq7> DOI: [10.1007/s12250-018-0064-8](https://doi.org/10.1007/s12250-018-0064-8) · PMID: [30374826](https://www.ncbi.nlm.nih.gov/pubmed/30374826) · PMCID: [PMC6235757](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6235757)

129. **Coronavirus vaccine development: from SARS and MERS to COVID-19** Yen-Der Li, Wei-Yu Chi, Jun-Han Su, Louise Ferrall, Chien-Fu Hung, T-C Wu *Journal of Biomedical Science* (2020-12) <https://doi.org/gmf6bk> DOI: [10.1186/s12929-020-00695-2](https://doi.org/10.1186/s12929-020-00695-2) · PMID: [33341119](https://www.ncbi.nlm.nih.gov/pubmed/33341119) · PMCID: [PMC7749790](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7749790)

130. **Production of recombinant subunit vaccines: protein immunogens, live delivery systems and nucleic acid vaccines** Sissela Liljeqvist, Stefan Ståhl *Journal of Biotechnology* (1999-07) <https://doi.org/d4g86c> DOI: [10.1016/s0168-1656(99)00107-8](https://doi.org/10.1016/s0168-1656(99)00107-8)

131. **Acellular Pertussis Vaccines and Pertussis Resurgence: Revise or Replace?** Clara Maria Ausiello, Antonio Cassone *mBio* (2014-07) <https://doi.org/ggj6mm> DOI: [10.1128/mbio.01339-14](https://doi.org/10.1128/mbio.01339-14) · PMID: [24917600](https://www.ncbi.nlm.nih.gov/pubmed/24917600) · PMCID: [PMC4056554](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4056554)

132. **Pertussis: Challenges Today and for the Future** James D Cherry *PLoS Pathogens* (2013-07-25) <https://doi.org/gg74fv> DOI: [10.1371/journal.ppat.1003418](https://doi.org/10.1371/journal.ppat.1003418) · PMID: [23935481](https://www.ncbi.nlm.nih.gov/pubmed/23935481) · PMCID: [PMC3723573](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3723573)

133. **Advancements in the development of subunit influenza vaccines** Naru Zhang, Bo-Jian Zheng, Lu Lu, Yusen Zhou, Shibo Jiang, Lanying Du *Microbes and Infection* (2015-02) <https://doi.org/gngp52> DOI: [10.1016/j.micinf.2014.12.006](https://doi.org/10.1016/j.micinf.2014.12.006) · PMID: [25529753](https://www.ncbi.nlm.nih.gov/pubmed/25529753) · PMCID: [PMC4336774](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4336774)

134. **Vaccines – COVID19 Vaccine Tracker** <https://covid19.trackvaccines.org/vaccines/>

135. **Recent advances in the production of recombinant subunit vaccines inPichia pastoris** Man Wang, Shuai Jiang, Yefu Wang *Bioengineered* (2016-04-08) <https://doi.org/ghqkt8> DOI: [10.1080/21655979.2016.1191707](https://doi.org/10.1080/21655979.2016.1191707) · PMID: [27246656](https://www.ncbi.nlm.nih.gov/pubmed/27246656) · PMCID: [PMC4927204](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4927204)

136. **Coronavirus Pandemic (COVID-19)** Hannah Ritchie, Edouard Mathieu, Lucas Rodés-Guirao, Cameron Appel, Charlie Giattino, Esteban Ortiz-Ospina, Joe Hasell, Bobbie Macdonald, Diana Beltekian, Max Roser *Our World in Data* (2020-03-05) <https://ourworldindata.org/covid-vaccinations>

137. **SARS-CoV-2 spike glycoprotein vaccine candidate NVX-CoV2373 immunogenicity in baboons and protection in mice** Jing-Hui Tian, Nita Patel, Robert Haupt, Haixia Zhou, Stuart Weston, Holly Hammond, James Logue, Alyse D Portnoff, James Norton, Mimi Guebre-Xabier, … Gale Smith *Nature Communications* (2021-01-14) <https://doi.org/gjh782> DOI: [10.1038/s41467-020-20653-8](https://doi.org/10.1038/s41467-020-20653-8) · PMID: [33446655](https://www.ncbi.nlm.nih.gov/pubmed/33446655) · PMCID: [PMC7809486](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7809486)

138. **The Coming Age of Insect Cells for Manufacturing and Development of Protein Therapeutics** Christine M Yee, Andrew J Zak, Brett D Hill, Fei Wen *Industrial & Engineering Chemistry Research* (2018-07-09) <https://doi.org/gd332h> DOI: [10.1021/acs.iecr.8b00985](https://doi.org/10.1021/acs.iecr.8b00985) · PMID: [30886455](https://www.ncbi.nlm.nih.gov/pubmed/30886455) · PMCID: [PMC6420222](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6420222)

139. **Phase 1–2 Trial of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine** Cheryl Keech, Gary Albert, Iksung Cho, Andreana Robertson, Patricia Reed, Susan Neal, Joyce S Plested, Mingzhu Zhu, Shane Cloney-Clark, Haixia Zhou, … Gregory M Glenn *New England Journal of Medicine* (2020-12-10) <https://doi.org/gg9q7d> DOI: [10.1056/nejmoa2026920](https://doi.org/10.1056/nejmoa2026920) · PMID: [32877576](https://www.ncbi.nlm.nih.gov/pubmed/32877576) · PMCID: [PMC7494251](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7494251)

140. **Safety and Efficacy of NVX-CoV2373 Covid-19 Vaccine** Paul T Heath, Eva P Galiza, David N Baxter, Marta Boffito, Duncan Browne, Fiona Burns, David R Chadwick, Rebecca Clark, Catherine Cosgrove, James Galloway, … Seth Toback *New England Journal of Medicine* (2021-09-23) <https://doi.org/gk3zvz> DOI: [10.1056/nejmoa2107659](https://doi.org/10.1056/nejmoa2107659) · PMID: [34192426](https://www.ncbi.nlm.nih.gov/pubmed/34192426) · PMCID: [PMC8262625](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8262625)

141. **Novavax COVID-19 vaccine Nuvaxovid approved by MHRA** GOV.UK <https://www.gov.uk/government/news/novavax-covid-19-vaccine-nuvaxovid-approved-by-mhra>

142. **EMA recommends Nuvaxovid for authorisation in the EU** EMA *European Medicines Agency* (2021-12-20) <https://www.ema.europa.eu/en/news/ema-recommends-nuvaxovid-authorisation-eu>

143. **Novavax Submits Request to the U.S. FDA for Emergency Use Authorization of COVID-19 Vaccine** Novavax Investor Relations <https://ir.novavax.com/2022-01-31-Novavax-Submits-Request-to-the-U-S-FDA-for-Emergency-Use-Authorization-of-COVID-19-Vaccine>

144. <https://ir.novavax.com/news-releases/news-release-details/novavax-announces-expanded-collaboration-and-license-agreement>

145. **Covid-19: Whatever happened to the Novavax vaccine?** Serena Tinari, Catherine Riva *BMJ* (2021-12-08) <https://doi.org/gp5bjj> DOI: [10.1136/bmj.n2965](https://doi.org/10.1136/bmj.n2965) · PMID: [34880071](https://www.ncbi.nlm.nih.gov/pubmed/34880071)

146. **Why is WHO pushing back on a Health Canada–approved Medicago SARS-CoV-2 vaccine?** Diana Duong, Lauren Vogel *Canadian Medical Association Journal* (2022-04-03) <https://doi.org/gp37s9> DOI: [10.1503/cmaj.1095992](https://doi.org/10.1503/cmaj.1095992) · PMID: [35379666](https://www.ncbi.nlm.nih.gov/pubmed/35379666) · PMCID: [PMC8985905](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8985905)

147. **Covifenz** Medicago <https://medicago.com/en/our-products/our-vaccines/covifenz-covid-19-vlp-vaccine/>

148. **Efficacy, immunogenicity, and safety of a plant-derived, quadrivalent, virus-like particle influenza vaccine in adults (18–64 years) and older adults (≥65 years): two multicentre, randomised phase 3 trials** Brian J Ward, Alexander Makarkov, Annie Séguin, Stéphane Pillet, Sonia Trépanier, Jiwanjeet Dhaliwall, Michael D Libman, Timo Vesikari, Nathalie Landry *The Lancet* (2020-11) <https://doi.org/gjn28x> DOI: [10.1016/s0140-6736(20)32014-6](https://doi.org/10.1016/s0140-6736(20)32014-6)

149. **Phase 1 randomized trial of a plant-derived virus-like particle vaccine for COVID-19** Brian J Ward, Philipe Gobeil, Annie Séguin, Judith Atkins, Iohann Boulay, Pierre-Yves Charbonneau, Manon Couture, Marc-André D’Aoust, Jiwanjeet Dhaliwall, Carolyn Finkle, … Nathalie Landry *Nature Medicine* (2021-05-18) <https://doi.org/gm7br3> DOI: [10.1038/s41591-021-01370-1](https://doi.org/10.1038/s41591-021-01370-1) · PMID: [34007070](https://www.ncbi.nlm.nih.gov/pubmed/34007070) · PMCID: [PMC8205852](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8205852)

150. [10.1056/NEJMoa2201300](https://10.1056/NEJMoa2201300)

151. **Medicago and GSK announce the approval by Health Canada of COVIFENZ®, an adjuvanted plant-based COVID-19 vaccine | GSK** <https://www.gsk.com/en-gb/media/press-releases/medicago-and-gsk-announce-the-approval-by-health-canada-of-covifenz/>

152. **Influenza virus-like particles produced by transient expression in<i>Nicotiana benthamiana</i>induce a protective immune response against a lethal viral challenge in mice** Marc-André D’Aoust, Pierre-Olivier Lavoie, Manon M-J Couture, Sonia Trépanier, Jean-Martin Guay, Michèle Dargis, Sébastien Mongrand, Nathalie Landry, Brian J Ward, Louis-P Vézina *Plant Biotechnology Journal* (2008-12) <https://doi.org/b8xqkk> DOI: [10.1111/j.1467-7652.2008.00384.x](https://doi.org/10.1111/j.1467-7652.2008.00384.x) · PMID: [19076615](https://www.ncbi.nlm.nih.gov/pubmed/19076615)

153. **Covid-19: WHO set to reject Canadian plant based vaccine because of links with tobacco industry** Owen Dyer *BMJ* (2022-03-28) <https://doi.org/gp37s8> DOI: [10.1136/bmj.o811](https://doi.org/10.1136/bmj.o811) · PMID: [35346968](https://www.ncbi.nlm.nih.gov/pubmed/35346968)

154. **Plant-derived virus-like particles as vaccines** Qiang Chen, Huafang Lai *Human Vaccines &amp; Immunotherapeutics* (2013-01) <https://doi.org/f4rrfj> DOI: [10.4161/hv.22218](https://doi.org/10.4161/hv.22218) · PMID: [22995837](https://www.ncbi.nlm.nih.gov/pubmed/22995837) · PMCID: [PMC3667944](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3667944)

155. **Efficacy and Safety of NVX-CoV2373 in Adults in the United States and Mexico** Lisa M Dunkle, Karen L Kotloff, Cynthia L Gay, Germán Áñez, Jeffrey M Adelglass, Alejandro Q Barrat Hernández, Wayne L Harper, Daniel M Duncanson, Monica A McArthur, Diana F Florescu, … *Cold Spring Harbor Laboratory* (2021-10-10) <https://doi.org/g5w9> DOI: [10.1101/2021.10.05.21264567](https://doi.org/10.1101/2021.10.05.21264567)

156. **Novavax Statement on UK and Mexico Phase 3 Clinical Trial Participants Considered Fully Vaccinated in the US** Novavax Investor Relations <https://ir.novavax.com/Novavax-Statement-on-UK-and-Mexico-Phase-3-Clinical-Trial-Participants-Considered-Fully-Vaccinated-in-the-US>

157. **Efficacy and Safety of a Recombinant Plant-Based Adjuvanted Covid-19 Vaccine** Karen J Hager, Gonzalo Pérez Marc, Philipe Gobeil, Ricardo S Diaz, Gretchen Heizer, Conrado Llapur, Alexander I Makarkov, Eduardo Vasconcellos, Stéphane Pillet, Fernando Riera, … Brian J Ward *New England Journal of Medicine* (2022-05-04) <https://doi.org/gp3zrx> DOI: [10.1056/nejmoa2201300](https://doi.org/10.1056/nejmoa2201300) · PMID: [35507508](https://www.ncbi.nlm.nih.gov/pubmed/35507508)

158. **Efficacy of NVX-CoV2373 Covid-19 Vaccine against the B.1.351 Variant** Vivek Shinde, Sutika Bhikha, Zaheer Hoosain, Moherndran Archary, Qasim Bhorat, Lee Fairlie, Umesh Lalloo, Mduduzi SL Masilela, Dhayendre Moodley, Sherika Hanley, … Shabir A Madhi *New England Journal of Medicine* (2021-05-20) <https://doi.org/gjzcxc> DOI: [10.1056/nejmoa2103055](https://doi.org/10.1056/nejmoa2103055) · PMID: [33951374](https://www.ncbi.nlm.nih.gov/pubmed/33951374) · PMCID: [PMC8091623](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8091623)

159. **Immunogenicity and Safety Following a Homologous Booster Dose of a SARS-CoV-2 recombinant spike protein vaccine (NVX-CoV2373): A Phase 2 Randomized Placebo-Controlled Trial** Raburn Mallory, Neil Formica, Susan Pfeiffer, Bethanie Wilkinson, Alex Marcheschi, Gary Albert, Heather McFall, Michelle Robinson, Joyce S Plested, Mingzhu Zhu, … *Cold Spring Harbor Laboratory* (2021-12-25) <https://doi.org/gp5bjd> DOI: [10.1101/2021.12.23.21267374](https://doi.org/10.1101/2021.12.23.21267374)

160. **The challenges of distributing COVID-19 vaccinations** Melinda C Mills, David Salisbury *EClinicalMedicine* (2021-01) <https://doi.org/gh77b5> DOI: [10.1016/j.eclinm.2020.100674](https://doi.org/10.1016/j.eclinm.2020.100674) · PMID: [33319186](https://www.ncbi.nlm.nih.gov/pubmed/33319186) · PMCID: [PMC7725651](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7725651)

161. **An ethical framework for global vaccine allocation** Ezekiel J Emanuel, Govind Persad, Adam Kern, Allen Buchanan, Cécile Fabre, Daniel Halliday, Joseph Heath, Lisa Herzog, RJ Leland, Ephrem T Lemango, … Henry S Richardson *Science* (2020-09-03) <https://doi.org/ghz7k6> DOI: [10.1126/science.abe2803](https://doi.org/10.1126/science.abe2803) · PMID: [32883884](https://www.ncbi.nlm.nih.gov/pubmed/32883884) · PMCID: [PMC8691258](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8691258)

162. **Vaccine optimization for COVID-19: Who to vaccinate first?** Laura Matrajt, Julia Eaton, Tiffany Leung, Elizabeth R Brown *Science Advances* (2021-02-05) <https://doi.org/ghz7k7> DOI: [10.1126/sciadv.abf1374](https://doi.org/10.1126/sciadv.abf1374) · PMID: [33536223](https://www.ncbi.nlm.nih.gov/pubmed/33536223) · PMCID: [PMC8128110](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8128110)

163. **Tracking Coronavirus Vaccinations Around the World** Josh Holder *The New York Times* (2021-01-29) <https://www.nytimes.com/interactive/2021/world/covid-vaccinations-tracker.html>

164. **One Vaccine Side Effect: Global Economic Inequality** Peter S Goodman *The New York Times* (2020-12-25) <https://www.nytimes.com/2020/12/25/business/coronavirus-vaccines-global-economy.html>

165. **International Collaboration to Ensure Equitable Access to Vaccines for COVID‐19: The ACT‐Accelerator and the COVAX Facility** MARK ECCLESTON‐TURNER, HARRY UPTON *The Milbank Quarterly* (2021-03-02) <https://doi.org/gh77cc> DOI: [10.1111/1468-0009.12503](https://doi.org/10.1111/1468-0009.12503) · PMID: [33650737](https://www.ncbi.nlm.nih.gov/pubmed/33650737) · PMCID: [PMC8014072](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8014072)

166. **Fair allocation mechanism for COVID-19 vaccines through the COVAX Facility** <https://www.who.int/publications/m/item/fair-allocation-mechanism-for-covid-19-vaccines-through-the-covax-facility>

167. **Global plan seeks to promote vaccine equity, spread risks** Kai Kupferschmidt *Science* (2020-07-31) <https://doi.org/gh77cd> DOI: [10.1126/science.369.6503.489](https://doi.org/10.1126/science.369.6503.489) · PMID: [32732400](https://www.ncbi.nlm.nih.gov/pubmed/32732400)

168. **Bloomberg - Are you a robot?** <https://www.bloomberg.com/tosv2.html?vid=&uuid=ddafcf1d-d623-11ec-aa43-4c565842736c&url=L2dyYXBoaWNzL2NvdmlkLXZhY2NpbmUtdHJhY2tlci1nbG9iYWwtZGlzdHJpYnV0aW9u>

169. **Vaccine Supply** <https://www.mea.gov.in/vaccine-supply.htm>

170. **Covaxin: India approves two Covid vaccines for children under 12** BBC News (2022-04-26) <https://www.bbc.com/news/world-asia-india-55748124>

171. **DCGI grants EUA to Corbevax for those aged 5-12, Covaxin for 6-12 age group** Tribune News Service *Tribuneindia News Service* <https://www.tribuneindia.com/news/nation/covaxin-cleared-for-6-12-age-group-by-drugs-regulator-389581>

172. **Novavax aims for 2 billion COVID-19 vaccine doses with expanded India deal** Reuters (2020-09-15) <https://www.reuters.com/article/health-coronavirus-novavax-idUSKBN2661PI>

173. **Intranasal Vaccine For Covid-19 | Bharat Biotech** <https://www.bharatbiotech.com/intranasal-vaccine.html>

174. **China Wanted to Show Off Its Vaccines. It’s Backfiring.** Sui-Lee Wee *The New York Times* (2021-01-25) <https://www.nytimes.com/2021/01/25/business/china-covid-19-vaccine-backlash.html>

175. **Coronavirus Vaccine Tracker** Carl Zimmer, Jonathan Corum, Sui-Lee Wee, Matthew Kristoffersen *The New York Times* (2020-06-10) <https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html>

176. **Coronavirus Vaccine Tracker** Carl Zimmer, Jonathan Corum, Sui-Lee Wee, Matthew Kristoffersen *The New York Times* (2020-06-10) <https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html>

177. **The US Regulatory System and COVID-19 Vaccines** Joshua M Sharfstein, Jesse L Goodman, Luciana Borio *JAMA* (2021-03-23) <https://doi.org/gh77b3> DOI: [10.1001/jama.2021.1961](https://doi.org/10.1001/jama.2021.1961) · PMID: [33587124](https://www.ncbi.nlm.nih.gov/pubmed/33587124)

178. **Chinese Omicron-specific mRNA COVID vaccine candidate to be trialed in UAE** Reuters *Reuters* (2022-04-30) <https://www.reuters.com/business/healthcare-pharmaceuticals/chinese-omicron-specific-mrna-covid-vaccine-candidate-be-trialed-uae-2022-04-30/>

179. **Philippines receives COVID-19 vaccine after delays** ABC News *ABC News* <https://abcnews.go.com/Health/wireStory/philippines-receive-covid-19-vaccine-delays-76163594>

180. **China’s Covid-19 Vaccine Makers Struggle to Meet Demand** Chao Deng in Taipei and Jared Malsin in Dubai *Wall Street Journal* (2021-02-10) <https://www.wsj.com/articles/chinas-covid-19-vaccine-makers-struggle-to-meet-demand-11612958560>

181. **With First Dibs on Vaccines, Rich Countries Have ‘Cleared the Shelves’** Megan Twohey, Keith Collins, Katie Thomas *The New York Times* (2020-12-15) <https://www.nytimes.com/2020/12/15/us/coronavirus-vaccine-doses-reserved.html>

182. **Solidarity across borders: A pragmatic need for global COVID‐19 vaccine equity** Denise N Obinna *The International Journal of Health Planning and Management* (2021-09-28) <https://doi.org/gnrkrh> DOI: [10.1002/hpm.3341](https://doi.org/10.1002/hpm.3341) · PMID: [34585430](https://www.ncbi.nlm.nih.gov/pubmed/34585430) · PMCID: [PMC8653338](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8653338)

183. **Zimbabwe authorizes use of India's first indigenous COVID-19 vaccine - Xinhua | English.news.cn** <http://www.xinhuanet.com/english/2021-03/04/c_139783893.htm>

184. **Covid-19 vaccinations: African nations miss WHO target** BBC News (2021-12-31) <https://www.bbc.com/news/56100076>

185. **First COVID-19 COVAX vaccine doses administered in Africa** <https://www.who.int/news/item/01-03-2021-first-covid-19-covax-vaccine-doses-administered-in-africa>

186. **Covax must go beyond proportional allocation of covid vaccines to ensure fair and equitable access** Lisa M Herzog, Ole F Norheim, Ezekiel J Emanuel, Matthew S McCoy *BMJ* (2021-01-05) <https://doi.org/gjgqjv> DOI: [10.1136/bmj.m4853](https://doi.org/10.1136/bmj.m4853) · PMID: [33402340](https://www.ncbi.nlm.nih.gov/pubmed/33402340)

187. **COVAX** <https://www.who.int/initiatives/act-accelerator/covax>

188. **Countries now scrambling for COVID-19 vaccines may soon have surpluses to donate** AAAS Articles DO Group *American Association for the Advancement of Science (AAAS)* (2021-08-16) <https://doi.org/gh77cf> DOI: [10.1126/science.abh4476](https://doi.org/10.1126/science.abh4476)

189. **Model-informed COVID-19 vaccine prioritization strategies by age and serostatus** Kate M Bubar, Kyle Reinholt, Stephen M Kissler, Marc Lipsitch, Sarah Cobey, Yonatan H Grad, Daniel B Larremore *Science* (2021-02-26) <https://doi.org/ght4xk> DOI: [10.1126/science.abe6959](https://doi.org/10.1126/science.abe6959) · PMID: [33479118](https://www.ncbi.nlm.nih.gov/pubmed/33479118) · PMCID: [PMC7963218](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7963218)

190. **Strategic spatiotemporal vaccine distribution increases the survival rate in an infectious disease like Covid-19** Jens Grauer, Hartmut Löwen, Benno Liebchen *Scientific Reports* (2020-12) <https://doi.org/ghq7vp> DOI: [10.1038/s41598-020-78447-3](https://doi.org/10.1038/s41598-020-78447-3) · PMID: [33299029](https://www.ncbi.nlm.nih.gov/pubmed/33299029) · PMCID: [PMC7726577](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7726577)

191. **How should we conduct pandemic vaccination?** Jane Williams, Chris Degeling, Jodie McVernon, Angus Dawson *Vaccine* (2021-02) <https://doi.org/gh77b7> DOI: [10.1016/j.vaccine.2020.12.059](https://doi.org/10.1016/j.vaccine.2020.12.059) · PMID: [33423839](https://www.ncbi.nlm.nih.gov/pubmed/33423839) · PMCID: [PMC7792561](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7792561)

192. **Vaccine ethics: an ethical framework for global distribution of COVID-19 vaccines** Nancy S Jecker, Aaron G Wightman, Douglas S Diekema *Journal of Medical Ethics* (2021-02-16) <https://doi.org/gh77cg> DOI: [10.1136/medethics-2020-107036](https://doi.org/10.1136/medethics-2020-107036) · PMID: [33593876](https://www.ncbi.nlm.nih.gov/pubmed/33593876) · PMCID: [PMC7887861](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7887861)

193. **Optimal SARS-CoV-2 vaccine allocation using real-time seroprevalence estimates in Rhode Island and Massachusetts** Thu Nguyen-Anh Tran, Nathan Wikle, Joseph Albert, Haider Inam, Emily Strong, Karel Brinda, Scott M Leighow, Fuhan Yang, Sajid Hossain, Justin R Pritchard, … Maciej F Boni *Cold Spring Harbor Laboratory* (2021-01-15) <https://doi.org/gh77b9> DOI: [10.1101/2021.01.12.21249694](https://doi.org/10.1101/2021.01.12.21249694) · PMID: [33469599](https://www.ncbi.nlm.nih.gov/pubmed/33469599) · PMCID: [PMC7814845](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7814845)

194. **Coronavirus Pandemic (COVID-19)** Hannah Ritchie, Edouard Mathieu, Lucas Rodés-Guirao, Cameron Appel, Charlie Giattino, Esteban Ortiz-Ospina, Joe Hasell, Bobbie Macdonald, Diana Beltekian, Max Roser *Our World in Data* (2020-03-05) <https://ourworldindata.org/covid-vaccination-policy>

195. **SARS Vaccine Development** Shibo Jiang, Yuxian He, Shuwen Liu *Emerging Infectious Diseases* (2005-07) <https://doi.org/gm2qkj> DOI: [10.3201/eid1107.050219](https://doi.org/10.3201/eid1107.050219) · PMID: [16022774](https://www.ncbi.nlm.nih.gov/pubmed/16022774) · PMCID: [PMC3371787](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3371787)

196. **A decade after SARS: strategies for controlling emerging coronaviruses** Rachel L Graham, Eric F Donaldson, Ralph S Baric *Nature Reviews Microbiology* (2013-11-11) <https://doi.org/ggwrzg> DOI: [10.1038/nrmicro3143](https://doi.org/10.1038/nrmicro3143) · PMID: [24217413](https://www.ncbi.nlm.nih.gov/pubmed/24217413) · PMCID: [PMC5147543](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5147543)

197. **Developing Covid-19 Vaccines at Pandemic Speed** Nicole Lurie, Melanie Saville, Richard Hatchett, Jane Halton *New England Journal of Medicine* (2020-05-21) <https://doi.org/ggq8bc> DOI: [10.1056/nejmp2005630](https://doi.org/10.1056/nejmp2005630) · PMID: [32227757](https://www.ncbi.nlm.nih.gov/pubmed/32227757)

198. **Vaccines for emerging infectious diseases: Lessons from MERS coronavirus and Zika virus** Joel N Maslow *Human Vaccines & Immunotherapeutics* (2017-08-28) <https://doi.org/gk7gb4> DOI: [10.1080/21645515.2017.1358325](https://doi.org/10.1080/21645515.2017.1358325) · PMID: [28846484](https://www.ncbi.nlm.nih.gov/pubmed/28846484) · PMCID: [PMC5718785](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5718785)

199. **2 Houston doctors nominated for Nobel Peace Prize for low-cost COVID vaccine** CultureMap Houston <https://houston.culturemap.com/news/innovation/02-02-22-dr-peter-hotez-nobel-peace-prize-dr-maria-elena-bottazzi-lizzie-fletcher/>