Vaccine Development Strategies for SARS-CoV-2

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## 0.1 Abstract

Vaccines have revolutionized the relationship between people and disease. In the 21st century, a number of emergent viruses have emphasized the importance of rapid and scalable vaccine development programs. During the pandemic caused by *Severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2), recent biotechnological advances in vaccine design provided the circumstances for the development and deployment of vaccines at an unprecedented pace. The genome sequence of SARS-CoV-2 was released on January 10th, 2020, allowing for global efforts in vaccine development to begin within two weeks of the international community becoming aware of the new viral threat. Both pre-existing vaccine platforms and novel vaccine technologies have been explored against SARS-CoV-2. Although historically a slow process, vaccine development in the face of COVID-19 accelerated so much that less than a year into the pandemic, some vaccine candidates had reported interim phase III clinical trial data and were being administered in countries around the world. In this review, we examine the strategies used to develop the leading vaccine candidates and where these candidates currently stand in terms of efficacy, safety, and approval in light of the ongoing pandemic and threat from emerging SARS-CoV-2 variants. We also discuss the patterns of distribution around the world. Vaccine development began almost five centuries ago, but the SARS-CoV-2 pandemic provides an exceptional illustration of how rapidly vaccine development technology has evolved in the last two decades.

## 0.2 Importance

The SARS-CoV-2 pandemic has caused untold damage to the global population, but it also presented some unique opportunities for vaccine development. As of September 18, 2021, SARS-CoV-2 has infected over 228,182,335 and cost the lives of 4,685,838 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. Now that promising candidates exist, effective deployment will provide an opportunity to move into a new phase of the pandemic where the susceptibility of worldwide populations is significantly reduced. This review provides a historical context for vaccine devleopment and highlights the main strategies utilized for the development of the COVID-19 vaccines, their clinical appraisal, and their distribution. These technologies have revolutionized the timescale at which countries can mount a response to an emerging viral threat and provide potential for mitigating future threats before their damage reaches the levels caused by SARS-CoV-2. As the SARS-CoV-2 virus has evolved, they also provide insight into how these technologies have to adapt on incredibly short timescales.

## 0.3 Introduction

The development of vaccines is widely considered one of the most important medical advances in recent human history. Over the past 150 years, approaches to vaccine developments have undergone a transformation and the diversity of available strategies has grown [[1](#ref-YY3x3bBV)]. Since the turn of the millennium, particular interest has emerged in the potential to develop vaccines as a rapid response to emerging threats. Severe acute respiratory syndrome (SARS), “swine flu” (H1N1), Middle East respiratory syndrome (MERS), and Ebola all underscored the importance of a rapid global response to a new infectious virus, but the vaccine development process has historically been slow, and vaccines fail to provide immediate prophylactic protection or treat ongoing infections [[2](#ref-181QWa7HL)]. However, the *Severe acute respiratory syndrome-related coronavirus 2* (SARS-CoV-2) pandemic has highlighted a confluence of circumstances that positioned vaccine development as a key player in efforts to control the virus and mitigate its damage. Examining the vaccine development programs tackling the COVID-19 pandemic alongside other 21st century efforts to control emerging viral threats demonstrates the significant biotechnological advances in this field.

## 0.4 Historical Vaccine Development

The first vaccination strategy in human history is widely considered to be the practice of variolation, which makes the history of vaccine development almost 500 years long [[3](#ref-Q10m9bJ),[4](#ref-1Clt2Bek3)]. Famously employed as a strategy to improve survival of smallpox by, for example, exposing a healthy individual to pus from smallpox pustules [[3](#ref-Q10m9bJ),[4](#ref-1Clt2Bek3),[5](#ref-ZUHALvLg)], variolation provides a mechanism for infecting a healthy individual with a mild case of a disease. This strategy aims to confer adaptive immunity, but it also carries a number of risks for the vaccine recipient [[6](#ref-kC2tx3JC)]. This approach was (debatably) the first example of a live-attenuated virus being used to induce immunity [[[6](#ref-kC2tx3JC)]; 10.1073/pnas.1400472111]. Many subsequent efforts to develop live-attenuated viral vaccines relied on either the identification of related zoonotic viruses that are less virulent in humans (e.g., cowpox/horsepox or rotavirus vaccines) or efforts to attenuate the virus through culturing it *in vitro* [[1](#ref-YY3x3bBV),[5](#ref-ZUHALvLg)]. This approach still carried risks, however [[1](#ref-YY3x3bBV)].

Efforts to overcome the limitations of live-virus vaccines led to the development of approaches to inactivate viruses (circa 1900) and to purify proteins from viruses cultured in eggs (circa 1920) [[1](#ref-YY3x3bBV),[7](#ref-dggZoRQD)]. Inactivated viral vaccines still raised some concerns, however, including that back-mutations could potentially lead the inactivated vaccines to become virulent or that recombination could occur between the inactivated virus and other viruses in circulation [[8](#ref-K0Ltu31S)]. For example, errors in the manufacturing process that produced polio vaccines containing live polio virus led to a polio outbreak in the United States [[9](#ref-AOgZug76)]. Concerns about contamination are shared across several vaccination platforms, including those that use live and attenuated viruses [[5](#ref-ZUHALvLg)]. Additionally, one of the major limitations of inactivated whole-virus vaccines is their susceptibility to lose efficacy due to mutations in the epitopes of the circulating virus [[8](#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.

With the increased feasibility of genetic research in the 1980s came the application of genetic engineering to vaccine development, which allowed for the growth of the gene sequences of specific viral antigens *in vitro* [[1](#ref-YY3x3bBV)]. While vaccine development strategies such as live-attenuation and inactivation remain in use in the 21st century [[1](#ref-YY3x3bBV)], approaches built off of the principles of genetic engineering offer some of the most dynamic opportunities in the field of modern vaccine development.

## 0.5 21st Century Advances in Vaccine Development



Figure 1: **Vaccine Development Strategies.** Several different strategies can and are being employed for the development of vaccines today. Each approach capitalizes on different features of the SARS-CoV-2 virus and delivery through a different platform. All of these approaches are being explored in the current pandemic.

While traditional methods of vaccine development such as inactivated whole viruses are still used today (Figure [1](#fig:vaccines)), biomedical research in the 21st century has been significantly influenced by the genomic revolution, and vaccine development is no exception. Building on the advances in vaccine development that came out of genetic engineering, several newer approaches to vaccine development today utilize information available in the DNA sequence of a virus (Figure [1](#fig:vaccines)).

In traditional DNA vaccines, the sequence encoding the antigen(s) against which an immune response is sought can be cultivated in a plasmid and delivered directly to an appropriate tissue [[10](#ref-XnrBoKVk)/]. Plasmids are not the only vector that can be used to deliver sequences associated with viral antigens: genetic material from the target virus can also be delivered using a second virus as a vector. Once the plasmid or viral vector brings the DNA sequence to an antigen presenting cell (APC), the host machinery can be used to construct antigen(s) from the transported genetic material, and the body can then synthesize antibodies in response [[11](#ref-BsrTDzJ2)].

More recently, interest has also emerged the potential for viral RNA to induce an immune response (Figure [1](#fig:vaccines)). This approach operates one level above the DNA: instead of directly furnishing the gene sequence associated with an antigen to the host, it provides the messenger RNA (mRNA) transcribed from the DNA sequence. Some of the potential advantages of mRNA compared to DNA include safety, as it cannot be integrated by the host and the half life can be regulated, it avoids any issues of a host immune response against the vector, and it holds the potential to dramatically accelerate vaccine manufacturing and development [[12](#ref-ENBWnhAh)].

These two appraoches are based on a similar underlying principle: utilizing a vector to deliver the information the host needs to produce an antigen, which in turn triggers an immune response to the antigen without introducing an infectious agent. In addition to lacking an infectious agent, both of these approaches are likely to offer several advantages over more traditional immunization platforms because they can stimulate both B- and T-cell responses [[11](#ref-BsrTDzJ2),[13](#ref-29LxSWHB)]. Current methods in vaccine development can therefore be framed in terms of the central dogma of genetics: instead of directly providing the proteins from the infectious agents, vaccines developers are exploring the potential for the delivery of DNA or RNA to induce the cell to produce proteins from the virus that in turn induce a host immune response.

All of these technologies are fairly new. Prior to 2020, no mRNA vaccines had been approved for use in humans, despite significant advances in the development of this technology [[12](#ref-ENBWnhAh)]. Vaccine development using mRNA is a recent frontier, with challenges in its execution arising from the instability of mRNA molecules, the design requirements of an efficient delivery system, and the potential for mRNA to elicit a very strong immune response [[12](#ref-ENBWnhAh)]. Therefore, while these technologies elegantly capitalize on decades of research in vaccine development as well as the tools of the genomic revolution, it was largely unknown prior to the SARS-CoV-2 pandemic whether this potential could be realized in a real-world vaccination effort.

## 0.6 The Pursuit of Rapid, Scalable Vaccine Development

The requirements for a successful vaccine trial and deployment are complex and may require coordination between government, industry, academia, and philanthropic entities [[14](#ref-plfPrQP7)]. Flu-like illnesses caused by viruses are a common target of vaccine development programs, and influenza vaccine technology in particular has made many strides. Beyond the seasonal flu, however, a number of emergent viral threats over the past 20 years have challenged the vaccine development pipeline to respond more rapidly to previously unknown viruses. During the H1N1 influenza outbreak, vaccine development was accelerated because of the existing infrastructure, along with the fact that regulatory agencies had already decided that vaccines produced using egg- and cell-based platforms could be licensed under the regulations used for a strain change. Critiques of the production and distribution of the H1N1 vaccine have stressed the need for alternative development-and-manufacturing platforms that can be readily adapted to new pathogens. Although a monovalent H1N1 vaccine was not available before the pandemic peaked in the United States and Europe, it was available soon afterward as a stand-alone vaccine that was eventually incorporated into commercially available seasonal influenza vaccines [[15](#ref-HyYY2agc)]. If H1N1 vaccine development provides any indication, considering developing and manufacturing platforms for promising COVID-19 vaccine trials early could hasten the emergence of an effective prophylactic vaccine against SARS-CoV-2. The potential for technologies such as DNA and RNA vaccines to benefit the field of oncology has encouraged vaccine developers to invest in next-generation approaches to vaccine development, which have led to the great diversity of vaccine development programs [[11](#ref-BsrTDzJ2),[16](#ref-wPl93ATP)].

## 0.7 Challenges and Opportunities in Developing a Vaccine against SARS-CoV-2

The emergence of SARS-CoV-2 in late 2019 rapidly induced a global public health crisis. This viral threat did not follow the same trajectory as other emergent viruses of recent note, such as SARS-CoV-1, MERS-CoV, and ebola virus, none of which reached the level of pandemic. Spread of the SARS-CoV-2 virus has remained out of control in many parts of the world well into 2021, especially with the emergence of variants that have increased rates of transmission [[17](#ref-r366f5T3)]. While, for a variety of reasons, SARS-CoV-2 was not controlled as rapidly as the viruses underlying prior 21st century epidemics, vaccine development technology had also progressed based on these and other prior viral threats to the point that a rapid international vaccine development response was possible. The first critical step towards developing a vaccine against SARS-CoV-2 was characterizing the viral target, which happened extremely early in the COVID-19 outbreak with the sequencing and dissemination of the viral genome in early January 2020 [[18](#ref-SvOLLYfw)/] (Figure [2](#fig:virus)). The *S* protein (Figure [2](#fig:virus)) is an antigen and induces an immune response [[19](#ref-Vnbw9o3T),[20](#ref-13wCBLnnu)]. <–To Do: insert discussion of pre vs post fusion conformation here->



Figure 2: **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 [[21](#ref-14FBejgLM)/] and the microscopy was conducted by the National Institute of Allergy and Infectious Diseases [[22](#ref-Jzj97hJh)].

For a highly infectious virus like SARS-CoV-2, a vaccine would hold particular value because it could bolster the immune response to the virus of the population broadly, thereby driving a lower rate of infection and likely significantly reducing fatalities. The Coalition for Epidemic Preparedness Innovations (CEPI) is coordinating global health agencies and pharmaceutical companies to develop vaccines against SARS-CoV-2. As of September 2020, there were over 180 vaccine candidates against SARS-CoV-2 in development [[23](#ref-dqpEe5Lz)]. While little is currently known about immunity to SARS-CoV-2, vaccine development typically tests for serum neutralizing activity, as this has been established as a biomarker for adaptive immunity in other respiratory illnesses [[24](#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 vaccine in phase III trials, where the effect of the vaccine on a cohort’s likelihood of contracting SARS-CoV-2 can be evaluated. Unlike many global vaccine development programs previously, such as with H1N1, the vaccine development landscape for COVID-19 includes vaccines produced by a wide array of technologies. These diverse technology platforms include DNA, RNA, virus-like particle, recombinant protein, both replicating and non-replicating viral vectors, live attenuated virus, and inactivated virus approaches (Figure [1](#fig:vaccines)).

## 0.8 Live-Attenuated Viruses

Live-attenuated vaccines (LAV), or 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 [[23](#ref-dqpEe5Lz)]. The virus can be attenuated by passaging it in a foreign host until, as a consequence of 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 [[23](#ref-dqpEe5Lz)]. LAVs are used globally to prevent diseases caused by viruses such as measles, rubella, polio, influenza, varicella zoster, and the yellow fever virus [[25](#ref-wZ2tXSUH)]. 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 [[6](#ref-kC2tx3JC),[26](#ref-zLL2yOJK),[27](#ref-7RHpaAHu)]. LAVs are also favored because they tend to be restricted to viral replication in the tissues around the location of inoculation [[28](#ref-iX8wXLPW)], and some can be administered intranasally [[23](#ref-dqpEe5Lz)].

The first deliberate attempt to utilize an attenuated viral vaccine dates back to Louis Pasteur in 1885, despite his not knowing that the disease-causing agent he was experimenting with was a virus. Indeed, the next intentional LAVs developed were intended to prevent illness caused by the yellow fever virus in 1935, followed by the first influenza vaccine in 1936 [[28](#ref-iX8wXLPW)]. Although LAV development strategies have the longest history, this strategy has not been widely utilized against SARS-CoV-2 and COVID-19. There is general concern that LAV strategies may risk causing disease in individuals who are immunocompromised [[29](#ref-bgKUtUIL)], which is an even greater concern when dealing with a novel virus and disease. Previously, there have been numerous attempts to develop both SARS-CoV-1 and MERS-CoV LAVs [[27](#ref-7RHpaAHu)], but no vaccines were approved for use in humans. While safety in production was a major concern in the past, nowadays manufacturers of LAVs 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.

There are at least five COVID-19 LAV candidates at various stages of vaccine development. A single-dose LAV candidate referred to as YF-SO used live-attenuated yellow fever 17D (YF17D) as a vector for a noncleavable prefusion conformation of the SARS-CoV-2 antigen. This LAV has been assessed in hamsters, mice, and macaques [[30](#ref-4RuaSyLg)]. YF-SO induced a robust immune response in all three animal models and prevented SARS-CoV-2 infection in macaques and hamsters [[30](#ref-4RuaSyLg)]. Other LAVs being investigated for the prophylaxis of COVID-19 include a Bacillus Calmette-Guerin (BCG) vaccine sponsored by institutes in Australia in collaboration with the Bill and Melinda Gates Foundation, which is in phase III clinical testing [[31](#ref-9m3rP633)]. A second investigation using a BCG vaccine is also ongoing, which is led by Texas A&M University in collaboration with numerous other U.S. institutions [[32](#ref-xdqxBruc)]. The purpose of the BCG vaccine is to prevent tuberculosis; however, it is known to exert protective non-specific effects against other respiratory tract infections in *in vitro* and *in vivo* studies [[33](#ref-16FOT89K5)], hence the interest many have for its potential use against COVID-19 [[34](#ref-1CJtdlM6d)].

In April 2020, it was announced that the Indian Immunologicals Ltd. and Griffith University Australia had partnered to develop codon de-optimized LAV [[35](#ref-nwyfEEPl)]; however, there have been no updates on the findings of their preclinical testing. Another codon de-optimized LAV is being developed by Mehmet Ali Aydinlar University and Acibadem Labmed Health Services A.S., which also has yet to report the findings of its preclinical tests [[36](#ref-iCUWeMfX)]. Following successful preclinical investigation [[37](#ref-xMxJTYge)], an intranasally administered deoptimized SARS-CoV-2 LAV known as COVI-VAC was developed by both New York-based Codagenix and the Serum Institute of India. COVI-VAC entered phase I human trials and dosed its first participants in January 2021 [[36](#ref-iCUWeMfX),[38](#ref-bPMpOwp8)].  
It is anticipated that the COVI-VAC phase I human trials will be completed by May 2022. Similarly, Meissa Vaccines in Kansas, U.S.A., which also develops vaccines for *Respiratory syncytial virus* (RSV), began enrollment for phase I human trials on an intranasal live-attenuated chimeric vaccine candidate in March 2021 for which recruitment is ongoing [[36](#ref-iCUWeMfX),[39](#ref-8ZMg94iW)].

Despite the long and trusted history of LAV development, this vaccine strategy does not appear to be favored for vaccine development against COVID-19. Modern technologies such as mRNA vaccines and vectored vaccines seem to have been favored due to their expediency and safety versus the time-consuming nature of developing LAVs using a novel virus.

## 0.9 Inactivated Whole-Virus Vaccines

Another well-established technology, inactivated whole-virus vaccines, is under development against SARS-CoV-2. This platform has been a valuable tool in efforts to control many viruses, and some well-known whole virus vaccines targets include influenza viruses, poliovirus, and hepatitis A virus. These types of vaccines use full virus particles that have been rendered non-infectious by chemical (i.e., formaldehyde or β-propiolactone [[40](#ref-PwjPrwXa)]) or physical (i.e., heat) means. Though these virus particles are inactivated, they still have the capacity to prime the immune system. The size of the virus particle makes it ideal for uptake by APC, which leads to stimulation of helper T-cells [[41](#ref-7Knbo28h)]. Additionally, the array of epitopes on the surface of the virus increases antibody binding efficiency [[41](#ref-7Knbo28h)]. The native conformation of the surface proteins, which is also important for eliciting an immune response, is preserved using these techniques. Membrane proteins, which support B-cell responses to surface proteins, are also included using this method [[42](#ref-iAa7uWOm)]. Overall, these vaccines are able to 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.

One prominent inactivated whole-virus vaccine against SARS-CoV-2 is being developed by Sinovac, a Beijing-based biopharmaceutical company. Their CoronaVac vaccine uses an inactivated whole virus with the addition of an aluminum adjuvant [[43](#ref-RGPoDfHS)] and is currently in Phase III clinical trials in Brazil [[44](#ref-KewHbkLZ)]. Phase I and II clinical trials indicated a strong immunogenic response in animal models and the development of neutralizing antibodies in human participants [[45](#ref-Ozya5HP5),[46](#ref-14fILrRWg),[47](#ref-N1txjPtt)]. Safety analysis of the vaccine during the phase II trial revealed that most adverse reactions were either mild (grade 1) or moderate (grade 2) in severity. The most common symptom was pain at the injection site (9%) and fever (3%), and only 2% (n=7) of participants participants reported severe adverse events, though these were determined to be unrelated to the vaccine. While data from the phase III study will be required to evaluate the efficacy of the virus under real-world conditions of exposure, the current results suggest that this vaccine is likely to adapt a well-established approach to vaccine development for the prevention of COVID-19.

India, the biggest producer of vaccines globally, has developed COVAXIN®, which is an indigenous COVID-19 vaccine researched and manufactured by Bharat Biotech International Ltd. in collaboration with the Indian Council of Medical Research (ICMR) - National Institute of Virology (NIV). Bharat Biotech reported 80.6% vaccine efficacy for its whole virion inactivated BBV152 (COVAXIN®) vaccine candidate in 25,800 participants in phase III clinical trials [[48](#ref-Ks3L7qHG),[49](#ref-DaDKZXdu)]. It was reported in *The Lancet* that the BBV152 vaccine candidate adjuvanted with alum and a Toll-like receptor 7/8 (TLR7/8) agonist is safe, immunogenic, and induces Th1-skewed memory T-cell responses upon immunization [[50](#ref-GxQSMH5l)]. Importantly, sera from individuals vaccinated with COVAXIN® efficiently neutralized the B.1.1.7 variant and the heterologous strain of SARS-CoV-2 [[51](#ref-VNckMunN)]. U.S.-based Ocugen Inc., a co-development partner of Bharat Biotech, is leading the application for an Emergency Use Authorization (EUA) for COVAXIN™ intended for the U.S. market. As of April 1, 2021 COVAXIN® has been approved for emergency use in Iran, Zimbabwe, and Nepal, and Mauritius and Paraguay have received a commercial supply of the vaccine. In Asia, China and India are the main COVID-19 vaccination developers and providers. Thus far, over 63 million people have been vaccinated against COVID-19 in India [[52](#ref-5xGlWp9l)/]. A broad range of COVID-19 vaccine candidates are under investigation in order to respond to the COVID-19 pandemic. In India, the Covaxin vaccine produced by Bharat Biotech received emergency authorization on January 3rd, 2021, despite the lack of phase III data until March 3rd [[48](#ref-Ks3L7qHG)]. Following the release of the phase III data indicating 81% efficacy, Zimbabwe authorized the use of Covaxin [[53](#ref-13yEnvOyP)]. In addition to COVAXIN®, Bharat Biotech has also developed an adenovirus vector-based intranasal BBV154 vaccine candidate that induces neutralizing IgG, mucosal IgA, and T cell responses [[54](#ref-P9mD7Gc9)]. In February, 2021, Bharat Biotech received approval from Indian officials to commence a phase I study of this intranasal chimpanzee-adenovirus (ChAd) vectored SARS-CoV-2-S vaccine [[54](#ref-P9mD7Gc9)]. Another Indian pharmaceutical industry, Zydus Cadila is developing India’s first indigenous DNA vaccine candidate ZyCoV-D [[55](#ref-o5iduzje)] which has completed phase I and II clinical trials and has received approval from Drugs Controller General of India (DCGI) to conduct a phase III clinical trial [[56](#ref-7f7eGud)]. Moreover, Indian-based Biological E.Limited has partnered with U.S.-based biopharmaceutical company Dynavax Technologies Corporation and Baylor College of Medicine, Texas, to initiate a phase I/II clinical trial in India for its COVID-19 subunit vaccine, which consists of the RBD of the spike protein of SARS-CoV-2 [[56](#ref-7f7eGud)]. Notably, Novavax has signed an agreement with the Serum Institute of India allowing them to produce up to 2 billion doses a year [[57](#ref-e8pnj0O3)]. Novavax has also signed agreements with the U.K., Canada, Australia, and South Korea [[58](#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 [[59](#ref-wByD9WaX)]. India has vaccinated approximately 24 million people [[60](#ref-DQmAgN0V)/]. This has been achieved by mainly using the AstraZeneca-University of Oxford vaccine, known as Covishield in India, which is also produced by the Serum Institute of India, and using India’s own Covaxin vaccine [[61](#ref-gsNWcXHn)]. India has also shipped approximately 58 million COVID-19 vaccines to 66 countries [[62](#ref-QRYET3sK)] Considering India produces approximately 60% of the world’s vaccines prior to the pandemic, it is no surprise that several other vaccine candidates are under development. These include ZyCov-Di, a DNA vaccine produced by Zydus Cadila, HGCO19, India’s first mRNA vaccine produced by Genova and HDT Biotech Corporation (of the U.S.), and the Bio E subunit vaccine produced by Biological E in collaboration with U.S.-based Dynavax and the Baylor College of Medicine [[61](#ref-gsNWcXHn)].

CoronaVac has been approved for use in China and has been granted emergency use in Azerbaijan, Brazil, Cambodia, Chile, Colombia, Ecuador, Hong Kong, Indonesia, Laos, Malaysia, Mexico, Philippines, Thailand, Turkey, Ukraine, and Uruguay [[63](#ref-ONBMyjqX)]. Sinovac has reported that their platform now has the capacity to provide up to a billion doses [[63](#ref-ONBMyjqX)]. The Sinopharm-Beijing Institute vaccine is currently approved for use in Bahrain, China, and the United Arab Emirates, but has been granted emergency use in Argentina, Cambodia, Egypt, Guyana, Hungary, Iran, Iraq, Jordan, Nepal, Pakistan, Peru, Venezuela, and Zimbabwe, with limited use in both Serbia and the Seychelles [[64](#ref-rqDwcy2A)]. 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 [[65](#ref-mR6133bK)]. 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 [[66](#ref-gdTtuj5e)]. Similar delays and shortages of doses promised have been reported by officials in the Philippines, Egypt, Morocco, and the United Arab Emirates [[67](#ref-XJmfG8HD),[68](#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 [[68](#ref-12zVLzkpB)].

## 0.10 Protein Subunit Vaccines

Compared to the inactivated whole virus vaccines, these protein subunit vaccines isolate a single protein of the virus and use it to stimulate the immune system. These proteins, also known as antigens, are usually those located on the surface of the viral particle and are therefore key targets of the immune system. These proteins are typically grown in yeast and then harvested. This vaccine can stimulate antibodies and CD4+ T-cell response [[69](#ref-12eGVhH5I)]. The main advantage of this method is that protein subunit vaccines are considered very safe, as the antigen alone cannot cause an infection. However, the immune response is weaker and an adjuvant is usually needed to boost the response [[70](#ref-mv42t1HV)] (see Appendix).

NVX-CoV2373, produced by U.S. company Novavax, is a protein nanoparticle vaccine candidate against SARS-CoV-2 that is constructed from a mutated prefusion SARS-CoV-2 spike protein in combination with a specialized adjuvant to elicit an immune response against SARS-CoV-2. The spike protein is recombinantly expressed in Sf9 insect cells [[71](#ref-Qk33ZrIC)], which have previously been used for several other FDA-approved protein therapeutics [[72](#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 [[71](#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 virus challenge, with particularly strong effects when administered with the proprietary adjuvant Matrix-MTM [[71](#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 [[73](#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. Although the phase III trial data has not been published yet, Novavax announced an efficacy of 89.3% based on their phase III trial in the UK and also noted that 90% of cases occurring in their phase IIb study in South Africa were caused by a variant of concern, B.1.351 [[74](#ref-YEkrZ5Pz)]. Despite these very preliminary results, Novavax has signed an agreement with the Serum Institute of India allowing them to produce up to 2 billion doses a year [[57](#ref-e8pnj0O3)] and has also signed agreements with the U.K., Canada, Australia, and South Korea [[58](#ref-X3fVa3P8)] as well as projecting that they will supply 1.1 billion doses to COVAX for distribution to countries with limited access to vaccine supplies [[59](#ref-wByD9WaX)].

## 0.11 Vaccines Delivering DNA

The delivery and presentation of antigens is fundamental to inducing immunity against a virus such as SARS-CoV-2. DNA vaccines offer an approach to delivering foreign substances into the body in a way that induces both a humoral and cellular immune response [[11](#ref-BsrTDzJ2)]. Delivering a DNA sequence to host cells allows the host to synthesize an antigen without exposure to a viral threat [[11](#ref-BsrTDzJ2)]. Host-synthesized antigens can then be presented in complex with major histocompatibility complex (MHC) I and II, which can activate either T- or B-cells [[11](#ref-BsrTDzJ2)]. While these vaccines encode specific proteins, providing many of the benefits of a protein subunit vaccine, they do not carry any risk of DNA being live, replicating, or spreading, and their manufacturing process lends itself to scalability [[11](#ref-BsrTDzJ2)]. Many of the safety concerns raised about DNA vaccines were not found to be an issue during preclinical and phase I testing, although antibiotic resistance introduced during the plasmid selection process remained a concern during this initial phase of development [[11](#ref-BsrTDzJ2)]. However, the immunogenicity of these vaccines has also not reached expectations [[11](#ref-BsrTDzJ2)].

### 0.11.1 DNA Vaccines

In the 1990s and 2000s, DNA vaccines delivered via plasmids sparked significant scientific interest, leading to a large number of preclinical trials [[11](#ref-BsrTDzJ2)]. Early preclinical trials primarily focused on long-standing disease threats, including viral diseases such as rabies and bacterial diseases such as malaria, and promising results led to phase I testing of the application of this technology to HIV, influenza, malaria, and other diseases of concern during this period [[11](#ref-BsrTDzJ2)]. Although they were well-tolerated, these early attempts to develop vaccines were generally not very successful in inducing immunity to the target pathogen, with either limited T-cell or limited neutralizing antibody responses observed [[11](#ref-BsrTDzJ2)].

Currently, a Phase I safety and immunogenicity clinical trial of INO-4800, a prophylactic vaccine against SARS-CoV-2, is underway [[75](#ref-xuzLfS0y)]. The vaccine developer Inovio Pharmaceuticals Technology is overseeing administration of INO-4800 by intradermal injection followed by electroporation with the CELLECTRA® device to healthy volunteers. Electroporation is the application of brief electric pulses to tissues in order to permeabilize cell membranes in a transient and reversible manner. It has been shown that electroporation can enhance vaccine efficacy by up to 100-fold, as measured by increases in antigen-specific antibody titers [[76](#ref-H6tWVs5R)]. The safety of the CELLECTRA® device has been studied for over seven years, and these studies support the further development of electroporation as a safe vaccine delivery method [[77](#ref-1Hsm2J1sc)]. The temporary formation of pores through electroporation facilitates the successful transportation of macromolecules into cells, allowing cells to robustly take up INO-4800 for the production of an antibody response. Approved by the United States (U.S.) FDA on April 6, 2020, the phase I study is enrolling up to 40 healthy adult volunteers in Philadelphia, PA at the Perelman School of Medicine and at the Center for Pharmaceutical Research in Kansas City, MO. The trial has two experimental arms corresponding to the two locations. Participants in Experimental Group 1 will receive one intradermal injection of 1.0 milligram (mg) of INO-4800 followed by electroporation using the CELLECTRA® 2000 device twice, administered at Day 0 and Week 4. Participants in Experimental Group 2 will receive two intradermal injections of 1.0 mg (total 2.0 mg per dosing visit) of INO-4800 followed by electroporation using the CELLECTRA® 2000 device, administered at Day 0 and Week 4. Safety data and the initial immune responses of participants from the trial are expected by the end of the summer of 2021. The development of a DNA vaccine against SARS-CoV-2 by Inovio could be an important step forward in the world’s search for a COVID-19 vaccine. Although exciting, the cost of vaccine manufacturing and electroporation may make scaling the use of this technology for prophylactic use for the general public difficult.

### 0.11.2 Viral-Vector DNA Vaccines

Viral vectors have emerged as a safe and efficient method to furnish the nucleotide sequences of an antigen to the immune system using a second virus as a vector [[78](#ref-1Ff2BDzkT)]. The genetic content of the vector virus is often altered to prevent it from replicating, but replication-competent viruses can also be used under certain circumstances [[79](#ref-1FpZkxdl4)]. The vaccine then uses the host machinery to construct antigen(s) from the transported genetic material, for which the body synthesizes antibodies in response. One of the early viral vectors explored was adenovirus, with serotype 5 (Ad5) being particularly effective [[11](#ref-BsrTDzJ2)]. This technology rose in popularity during the 2000s due to its being more immunogenic in humans and non-human primates than plasmid-vectored DNA vaccines [[11](#ref-BsrTDzJ2)]. In the 2000s, interest also arose in utilizing simian adenoviruses as vectors because of the reduced risk that human vaccine recipients would have prior exposure resulting in adaptive immunity [[11](#ref-BsrTDzJ2),[80](#ref-XRmk1S6R)], and chimpanzee adenoviruses were explored as a potential vector in the development of a vaccine against *Middle East respiratory syndrome-related coronavirus* (MERS-CoV) [[81](#ref-Jkm7jfS8)]. Today, various viral-vector platforms including poxviruses [[82](#ref-8bpbvIro),[83](#ref-1AZfAQ5py)], adenoviruses [[84](#ref-zX5UKhti)], and vesicular stomatitis viruses [[85](#ref-SNwg8Qkf),[86](#ref-lvi4DH2g)] are being developed, Viral-vector vaccines are able to induce both an antibody and cellular response; however, the response is limited due to the immunogenicity of the viral vector used [[84](#ref-zX5UKhti),[87](#ref-YRgRziXN)]. An important consideration in identifying potential vectors is the immune response to the vector. Both the innate and adaptive immune responses can potentially respond to the vector, limiting the ability of the vaccine to transfer information to the immune system [[88](#ref-tbs2wD7F)]. Different vectors are associated with different levels of reactogenicity; for example, adenoviruses elicit a much stronger innate immune response than replication deficient adeno-associated viruses derived from parvoviruses [[88](#ref-tbs2wD7F)]. Additionally, using a virus circulating widely in human populations as a vector presents additional challenges because vaccine recipients may already have developed an immune response to the vector [[89](#ref-IUplTKEg)].

There are several viral vector vaccines that are available for veterinary use [[11](#ref-BsrTDzJ2),[90](#ref-MvKb0qJC)], but prior to the COVID-19 pandemic, only one viral vector vaccine was approved by the FDA for use in humans. This vaccine is vectored with a recombinant vesicular stomatitis virus and targeted against the ebola virus [doi:10.1016/j.cell.2020.03.011]. Additionally, several phase I and phase II clinical trials for other vaccines are ongoing [[78](#ref-1Ff2BDzkT)], and the technology is currently being explored for its potential against numerous infectious diseases including malaria [[91](#ref-OZJWUaDW),[92](#ref-3tkGuMXx)], ebola [[93](#ref-AgZwwt5u),[94](#ref-9BEMTYn8),[95](#ref-PbGQOOI)], and human immunodeficiency virus (HIV) [[96](#ref-1C8hgfvDF),[97](#ref-SAIfGNkZ)]. The threat of MERS and SARS initiated interest in the application of viral vector vaccines to human coronaviruses [[81](#ref-Jkm7jfS8)], but efforts to apply this technology to these pathogens had not yet led to a successful vaccine candidate. In the mid-to-late 00s, adenoviral vectored vaccines against SARS were found to induce SARS-CoV-specific IgA in the lungs of mice [[98](#ref-umEOWDY5)], but were later found to offer incomplete protection in ferret models [[99](#ref-DGTFML2b)]. Gamaleya National Center of Epidemiology and Microbiology in Moscow sought to use an adenovirus platform for the development of vaccines for *Middle East respiratory syndrome-related coronavirus* and Ebola virus, although neither of the previous vaccines were internationally licensed [[100](#ref-UCI0TCHy)].

In 2017, results were published from an initial investigation of two vaccine candidates against MERS-CoV containing the MERS-CoV S gene vectored with chimpanzee adenovirus, Oxford University #1 (ChAdOx1), a replication-deficient chimpanzee adenovirus [[101](#ref-P94sxWp4)]. This study reported that a candidate containing the complete spike protein sequence induced a stronger neutralizing antibody response in mice than candidates vectored with modified vaccinia virus Ankara. It was pursued in additional research, and in the summer of 2020 results of two studies were published. The first reported that a single dose of ChAdOx1 MERS induced an immune response and inhibited viral replication in macaques [[102](#ref-3NtMBDMM)]. The second reported promising results from a phase I trial that administered the vaccine to adults and measured safety/tolerability and immune response (as indicated through immune assays following vaccination) [[103](#ref-ERfSJf5B)].

While not all of these results were available at the time that vaccine development programs against SARS-CoV-2 began, at least three viral vector vaccines have also been developed against this hCoV. First, collaboration between AstraZeneca and researchers at the University of Oxford has successfully applied a viral vector approach to the development of a vaccine against SARS-CoV-2 using the replication-deficient ChAdOx1 vector modified to encode the spike protein of SARS-CoV-2 [[104](#ref-1037p4Gvs)]. In phase I and I/II trials, respectively, the immunogenic potential of vaccine candidate ChAdOx1 nCoV-19 was demonstrated through the immune challenge of two animal models, mice and rhesus macaques [[104](#ref-1037p4Gvs)] and patients receiving the ChAdOx1 nCoV-19 vaccine developed antibodies to the SARS-CoV-2 spike protein that peaked by day 28, with these levels remaining stable until a second observation at day 56 [[105](#ref-2bBVSpM)]. In December 2020, preliminary results of the phase III trial were released detailing randomized control trials conducted in the U.K., Brazil, and South Africa between April and November 2020 [[19](#ref-Vnbw9o3T)]. These trials again compared ChAdOx1 nCoV-19 to a control, but the design of each study varied; pooling data across studies indicated an overall efficacy of 70.4%. ChAdOx1 nCoV-19 was first approved for emergency use on December 30, 2020 in the United Kingdom [[106](#ref-1A7PjhDDR)] and has since then been approved for emergency use in several dozen countries, in addition to receiving full approval in Brazil.

Second, a viral vector approach was also applied by Gamaleya to develop Sputnik V, a replication-deficient recombinant adenovirus (rAd) vaccine that combines two adenovirus vectors, rAd26-S and rAd5-S, that express the full-length SARS-CoV-2 spike glycoprotein. The two vectors are administered intramuscularly administered sequentially, following a prime-boost regimen. Despite a lack of data from clinical trials, President Vladimir Putin of Russia announced the approval of the Sputnik V vaccines on August 11th, 2020 [[107](#ref-3KMxmQhV)] and it has subsequently been administered in Russia and other countries. Subsequently, the phase I/II clinical trial was published and indicated that the vaccine was safe, with the most common adverse events being mild pain at the injection site (58%), hypothermia (50%), headaches (42%), fatigue (28%), and joint and muscle pain (24%), and immunogenic, with seroconversion observed in all participants three weeks after the second dose and with all participants producing antibodies to the SARS-CoV-2 glycoprotein [[108](#ref-PNZEiId1)]. In February 2021, six months after its approval in Russia, interim results of the phase III trial were released, indicating an overall vaccine efficacy of 91.6% for symptomatic COVID-19 [[109](#ref-gLAIyAHm)]. As of early January, Sputnik V had been administered to as many as 1.5 million Russians [[110](#ref-X5LkVfY6)/] , and doses of Sputnik V have also been distributed to other parts of Europe, such as Belarus, Bosnia-Herzegovina, Hungary, San Marino, Serbia, and Slovakia [[111](#ref-16LczMwFO),[112](#ref-Z0V7NK7Y),[113](#ref-16GYKbrOq)], with the Czech Republic and Austria also having expressed interest in its procurement [[114](#ref-125VEHWS7)].

Third, Janssen Pharmaceuticals, Inc., a subsidiary of Johnson & Johnson, also developed a viral vector vaccine in collaboration with and funded by the United States’s “Operation Warp Speed” [[115](#ref-D3Px25HN),[116](#ref-57BTbcko)]. The vaccine candidate JNJ-78436735, formerly known as Ad26.COV2-S, is a monovalent vaccine that is composed of a replication-deficient adenovirus serotype 26 (Ad26) vector expressing the stabilized prefusion S protein of SARS-CoV-2 [[117](#ref-pWf2T8J8),[118](#ref-10UC562ga)]. Unlike the other two viral vector vaccines available to date, JNJ-78436735 requires only a single dose, a characteristic that is expected to aid in global deployment [[119](#ref-gOOBv1MD)]. JNJ-78436735 was selected from among a number of initial candidate designs [[118](#ref-10UC562ga)] and tested *in vivo* in Syrian golden hamsters and Rhesus macaques to assess safety and immunogenicity [[118](#ref-10UC562ga),[119](#ref-gOOBv1MD),[120](#ref-HmMIiIv2),[121](#ref-EpOXYGt4)]. The JNJ-78436735 candidate was selected for its favorable immunogenicity profile and ease of manufacturability [[118](#ref-10UC562ga),[119](#ref-gOOBv1MD),[120](#ref-HmMIiIv2),[121](#ref-EpOXYGt4)] and was found to confer protection against SARS-CoV-2 in macaques even after six months [[122](#ref-HGVDPMLm)]. The one- versus two-dose regimen was tested in volunteers through a phase I/IIa trial [[117](#ref-pWf2T8J8)], although these results are not yet available; however, the study did report that the vaccine was well-tolerated and that most participants demonstrated seroconversion in a neutralization assay 29 days after immunization [[117](#ref-pWf2T8J8)]. The phase III trial is ongoing across several countries (Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, and the U.S.), but interim results were reported in a press release on January 29th, 2021 [[123](#ref-iWMHpTBJ),[124](#ref-1FcpboRMm)]. The vaccine was well-tolerated, and across all regions studied, it was found to be 66% effective after 28 days for the prevention of moderate to severe COVID-19 and to be 85% effective for the prevention of laboratory-confirmed severe COVID-19 as well as 100% protection against COVID-19-related hospitalization and death. However, the reported efficacy ranged from 57% in South Africa to 72% in the United States, suggesting that these observations might be influenced by the prominent viral strains circulating in each country at the time of the trial; at the time, several variants of concern including B.1.351, which was first identified in South Africa [[125](#ref-sqhvCTIL)], were being monitored.

The three viral-vector vaccines described above have demonstrated the potential for this technology to facilitate a quick response to an emerging pathogen. However, two of the three vaccines have faced a number of criticisms surrounding the implementation of their clinical trials. <–To Do: Suggestion to move some of the Sputnik controversy here, along with describing the issues with the AstraZeneca trial–> Additionally, though the vaccines are developed using similar principles, there are some differences that might influence their efficacy as SARS-CoV-2 evolves. In the Janssen vaccine, the S protein immunogen is stabilized in its prefusion conformation, while in the Sputnik V and AstraZeneca vaccines, it is not. The prefusion conformation of the SARS-CoV-2 S protein is metastable [[126](#ref-R7Xdh5nH)], and the release of energy during membrane fusion drives this process forward following destabilization [[127](#ref-17DSmRo9H),[128](#ref-3uddYea8)]. Due to the significant conformational changes that occur during membrane fusion [[129](#ref-qcVbT0w4),[130](#ref-hIc3bKWe),[131](#ref-zK0rFpz1)], S protein immunogens that are stabilized in the prefusion conformation are of particular interest, especially because a prefusion stabilized MERS-CoV S antigen was found to elicit an improved antibody response [[132](#ref-oghHqZDt)]. Moreover, the prefusion conformation offers an opportunity to target S2, a region of the S protein that accumulates mutations at a slower rate [[132](#ref-oghHqZDt),[133](#ref-13wWdgODZ),[134](#ref-OVsxrEuX)] (see also [[17](#ref-r366f5T3)]). Vaccine developers can use versions of the spike protein that contain mutations that stabilize the prefusion conformer, essentially locking them in this position [[135](#ref-lvq9hGmj)]. The immune response to the spike protein when it is stabilized in this conformation is improved over other S structures [[118](#ref-10UC562ga)]. Thus, vaccines that use this prefusion stabilized conformation, including the Janssen viral-vector vaccine, the Novavax-CoV2373 protein nanoparticle vaccine, as well as the Moderna and Pfizer/BioNTech mRNA vaccines, are expected to not only offer improved immunogenicity, but also be more resilient to the accumulation of mutations in SARS-CoV-2. How these differences in design influence the efficacy of these three viral-vector vaccines over time remains to be seen.

## 0.12 RNA Vaccines

Building on DNA Vaccine technology, RNA vaccines are an even more recent advancement for vaccine development. RNA vaccines are nucleic-acid based modalities that code for viral antigens against which the human body elicits a humoral and cellular immune response. The mRNA technology is transcribed *in vitro* and delivered to cells via lipid nanoparticles (LNP) [[136](#ref-HCImhzy8)]. They are recognized by ribosomes *in vivo* and then translated and modified into functional proteins [[8](#ref-K0Ltu31S)]. The resulting intracellular viral proteins are displayed on surface MHC proteins, provoking a strong CD8+ T cell response as well as a CD4+ T cell and B cell-associated antibody responses [[8](#ref-K0Ltu31S)]. Naturally, mRNA is not very stable and can degrade quickly in the extracellular environment or the cytoplasm. The LNP covering protects the mRNA from enzymatic degradation outside of the cell [[137](#ref-zNKWlCwE)]. Codon optimization to prevent secondary structure formation and modifications of the poly-A tail as well as the 5’ untranslated region to promote ribosomal complex binding can increase mRNA expression in cells. Furthermore, purifying out double-stranded RNA and immature RNA with FPLC (fast performance liquid chromatography) and HPLC (high performance liquid chromatography) technology will improve translation of the mRNA in the cell [[8](#ref-K0Ltu31S),[138](#ref-pRoqjur8)].

There are three types of RNA vaccines: non-replicating, *in vivo* self-replicating, and *in vitro* dendritic cell non-replicating [[139](#ref-1EM5nGaYd)]. Non-replicating mRNA vaccines consist of a simple open reading frame (ORF) for the viral antigen flanked by the 5’ UTR and 3’ poly-A tail. *In vivo* self-replicating vaccines encode a modified viral genome derived from single-stranded, positive sense RNA alphaviruses [[8](#ref-K0Ltu31S),[138](#ref-pRoqjur8)]. The RNA genome encodes the viral antigen along with proteins of the genome replication machinery, including an RNA polymerase. Structural proteins required for viral assembly are not included in the engineered genome [[8](#ref-K0Ltu31S)]. Self-replicating vaccines produce more viral antigens over a longer period of time, thereby evoking a more robust immune response [[139](#ref-1EM5nGaYd)]. Finally, *in vitro* dendritic cell non-replicating RNA vaccines limit transfection to dendritic cells. Dendritic cells are potent antigen-presenting immune cells that easily take up mRNA and present fragments of the translated peptide on their MHC proteins, which can then interact with T cell receptors. Ultimately, primed T follicular helper cells can stimulate germinal center B cells that also present the viral antigen to produce antibodies against the virus [[140](#ref-3LMMW7F0)]. These cells are isolated from the patient, grown and transfected *ex vivo*, and reintroduced to the patient [[12](#ref-ENBWnhAh)].

Vaccines based on mRNA delivery confer many advantages over traditional viral vectored vaccines and DNA vaccines. In comparison to live attenuated viruses, mRNA vaccines are non-infectious and can be synthetically produced in an egg-free, cell-free environment, thereby reducing the risk of a detrimental immune response in the host [[141](#ref-wYZ6qJMu)]. Unlike DNA vaccines, mRNA technologies are naturally degradable and non-integrating, and they do not need to cross the nuclear membrane in addition to the plasma membrane for their effects to be seen [[8](#ref-K0Ltu31S)]. Furthermore, mRNA vaccines are easily, affordably, and rapidly scalable. Although mRNA vaccines have been developed for therapeutic and prophylactic purposes, none have previously been licensed or commercialized. Nevertheless, they have shown promise in animal models and preliminary clinical trials for several indications, including rabies, coronavirus, influenza, and cytomegalovirus [[142](#ref-3EUiWZdN)]. Preclinical data previously identified effective antibody generation against full-length FPLC-purified influenza hemagglutinin stalk-encoding mRNA in mice, rabbits, and ferrets [[143](#ref-6wZy2mn8)]. Similar immunological responses for mRNA vaccines were observed in humans in Phase I and II clinical trials operated by the pharmaceutical-development companies Curevac and Moderna for rabies, flu, and zika [[138](#ref-pRoqjur8)]. Positively charged bilayer LNPs carrying the mRNA attract negatively charged cell membranes, endocytose into the cytoplasm [[137](#ref-zNKWlCwE)], and facilitate endosomal escape. LNPs can be coated with modalities recognized and engulfed by specific cell types, and LNPs that are 150 nm or less effectively enter into lymphatic vessels [[137](#ref-zNKWlCwE),[144](#ref-Djz8x39x)]. Therefore, this technology holds great potential for targeted delivery of modified mRNA.

Given the potential for this technology to be quickly adapted for a new pathogen, it has held significant interest for the treatment of COVID-19. In the vaccines developed under this approach, the mRNA coding for a stabilized prefusion spike protein, which is immunogenic [[145](#ref-5x25saIz)], can be furnished to the immune system in order to train its response. Two vaccine candidates in this category emerged with promising phase III results at the end of 2020. Both require two doses approximately one month apart. The first was Pfizer/BioNTech’s BNT162b2, which contains the full prefusion stabilized, membrane-anchored SARS-CoV-2 spike protein in a vaccine formulation based on modified mRNA (modRNA) technology [[146](#ref-1CsCQi9wT),[147](#ref-10VyxCgQU)]. In the phase II/III multinational trial, this vaccine was associated with a 95% efficacy against laboratory-confirmed COVID-19 and with mild-to-moderate local and systemic effects but a low risk of serious adverse effects [[148](#ref-CWlYjjIV)]. Similarly, ModernaTX developed mRNA-1273, which, despite being the second mRNA vaccine to release phase III results, was the first mRNA vaccine to enter phase I clinical trials. mRNA-1273 is comprised by a conventional lipid nanoparticle encapsulated RNA encoding a full-length prefusion stabilized S protein for SARS-CoV-2 [[149](#ref-Biu1CQeQ)]. In the phase I trial, neutralizing activity reached similar levels to that observed in convalescent plasma samples by day 7 after the second dose of RNA-1273 [[24](#ref-wiGjCZC8)]. A few months later, interim results from the phase III trial indicated 94.5% efficacy of the vaccine in preventing symptomatic COVID-19 in adults who received the vaccine at 99 sites around the United States [[150](#ref-ZYxoabEm)]. Similar to BNT162b2, the vaccine was associated with mild-to-moderate adverse effects but with a low risk of serious adverse events [[150](#ref-ZYxoabEm)]. In late 2020, both vaccines both received approval from the United States’s Food and Drug Administration (FDA) under an emergency use authorization [[151](#ref-cAaN4Te0),[152](#ref-13Ou1UUAd)], and these vaccines have been widely distributed, primarily in North America and the European Union [[59](#ref-wByD9WaX)]. As the first mRNA vaccines to make it to market, these two highly efficacious vaccines demonstrate the power of this emerging technology, which has previously attracted scientific interest because of its potential to be used to treat non-infectious as well as infectious diseases.

## 0.13 Discussion (Probably to be fleshed out into multiple sections)

Given the wide range of vaccines under development, it is possible that some vaccine products may eventually be shown to be more effective in certain subpopulations, such as children, pregnant women, immunocompromised patients, the elderly, etc. However, the vaccine development process has historically been slow, and vaccines fail to provide immediate prophylactic protection or treat ongoing infections [[2](#ref-181QWa7HL)].

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

# 1 Vaccine Development Strategies for SARS-CoV-2

### 1.0.1 Appendix: Sinovac’s CoronaVac

Pre-clinical trials were performed using BALB/c mice and rhesus macaques [[46](#ref-14fILrRWg)]. The SARS-CoV-2 strains used in this trial isolated from 11 hospitalized patients (5 from China, 3 from Italy, 1 from the UK, 1 from Spain, 1 from Switzerland). A phylogenetic analysis demonstrated that the strains were representative of the current circulating variants. One of the strains, CN2, from China was used as the inactivated and purified virus while the other 10 strains were used to challenge. The CN2 was grown in Vero cells. An ELISA assay was used to assess the immunogenicity of the vaccine. 10 mice were injected with the vaccine on day 0 and day 7 with varying doses (0, 1.5, 3 or 6 μg), and 10 mice were treated with physiological saline as the control. IgG developed in the serum of all vaccinated mice. Using the same setup, immunogenicity was also assessed in macaques. Four macaques were assigned to each of four groups: treatment with 3 μg at day 0, 7 and 14, treatment with a high dose of 6 μg at day 0, 7 and 14, administration of a placebo vaccine, and administration of only the adjuvant. All vaccinated macaques induced IgGs and neutralizing antibodies. After challenge with SARS-CoV-2 strain CN1, vaccinated macaques were protected compared to control macaques (placebo or adjuvant only) based on histology and viral loads collected from different regions of the lung.

Phase I/II clinical trials were conducted in adults 18-59 years old [[47](#ref-N1txjPtt)] and adults over 60 years old [[45](#ref-Ozya5HP5)] in China. In the case of adults 18-59 years old, a single center, randomized, double-blind, placebo-controlled phase I/II trial was conducted in April 2020. Patients in this study were recruited from the community in Suining County of Jiangsu province, China. For the phase I trial, 144 (of 185 screened) participants were enrolled, with 72 enrolled in the 14-day interval cohort (i.e., treated on day 0 and day 14) and 72 in the 28-day interval cohort. This group of 72 participants was split into 2 blocks for a low-dose (3 μg) and high-dose (6 μg) vaccine. Within each block, participants were randomly assigned vaccination with CoronaVac or placebo (aluminum diluent without the virus) at a 2:1 ratio. Both the vaccine and placebo were prepared in a Good Manufacturing Practice-accredited facility of Sinovac Life Sciences (Beijing, China).

The phase II trial followed the same organization of participants, this time using 300 enrolled participants in the 14-day and another 300 enrolled in the 28-day groups. One change of note was that the vaccine was produced using a highly automated bioreactor (ReadyToProcess WAVE 25, GE, Umeå, Sweden) to increase vaccine production capacity. This change resulted in a higher intact spike protein content. The authors of this study were not aware of this antigen-level difference between the vaccine batches for the phase I/II when the ethical approval for the trials occurred.

To assess adverse responses, participants were asked to record any events up to 7 days post-treatment. The reported adverse events were graded according to the China National Medical Products Administration guidelines. In the phase I trial, the overall incidence of adverse reactions was 29-38% of patients in the 0 to 14 day group and 13-17% in the 0 to 28 day vaccination group. The most common symptom was pain at the injection site, which was reported by 17-21% of patients in the 0 to 14 day cohort and 13% in the 0 to 28 day cohort. Most adverse reactions were mild (grade 1) where patients recovered within 48 hours. A single case of acute hypersensitivity with manifestation of urticaria 48 hours following the first dose of study drug was reported in the 6 μg group Most adverse reactions were mild (grade 1) in severity and participants recovered within 48 hours. There was a single case, from the 6 μg group, of acute hypersensitivity with manifestation of urticaria 48 hours after the first dose. Both the 14-day and 28-day cohorts had a strong neutralizing Ab response. The neutralizing Ab response was measured using a micro cytopathogenic effect assay, which assesses the minimum dilution of neutralizing Ab to be 50% protective against structural changes in host cells in response to viral infection [[153](#ref-1GUVvcQjL)]. Additionally IgG antibody titers against the receptor binding domain were also measured using ELISA.

Another phase I/II study was performed with older patients (older than 60 years) [[45](#ref-Ozya5HP5)]. The study conducted a single-center, randomized, double-blind, placebo-controlled trial. The phase I trial looked at dose escalation using 3 dosages: 1.5, 3 and 6 μg. The mean age of participants was 65.8 years (std = 4.8). Of 95 screened participants, 72 were enrolled. These 72 participants were split into low (3 μg) and high (6 μg) dose groups. Within each group, 24 participants received the treatment and 12 the placebo. A neutralizing antibody response against live SARS-CoV-2 was detected compared to baseline using the same micro cytopathogenic effect assay. This response was similar across the two dose concentrations. Additionally, they did not observe a difference in response between age groups (60–64 years, 65–69 years, and ≥70 years).

In phase II the mean age was 66.6 years (standard deviation = 4.7). 499 participants were screened and 350 were enrolled. 300 were evenly split into 1.5, 3 and 6 μg dose groups, and the remaining 50 were assigned to the placebo group. Again, they found a neutralizing antibody response in phase II. There wasn’t a significant different between the response to 3 μg versus 6 μg, but the response was higher than that to 1.5 μg.

Participants were required to record adverse reaction events within the first 7 days after each dose. The safety results were combined across phage I and II. All adverse reactions were either mild (grade 1) or moderate (grade 2) in severity. The most common symptom was pain at the injection site (9%) and fever (3%). 2% (7 participants) reported severe adverse events (4 from the 1.5 μg group, 1 from the 3 μg group, 2 from the 6 μg group), though these were found to be unrelated to the vaccine.

Overall, the results from the pre-clinical and phase I/II clinical trials are promising. It was also very hopeful to see that the immune response was consistent in older adults (> 60 years). Currently, phase III trials are being conducted in Brazil [[44](#ref-KewHbkLZ)]. This is a randomized, multicenter, endpoint driven, double-blind, placebo-controlled clinical trial. They are expecting 13,060 participants with 11,800 ages 18 to 59 years and 1,260 age 60+. Participants will be health care professionals.

## 1.1 RNA Vaccines

RNA vaccines are nucleic-acid based modalities that code for viral antigens against which the human body elicits a humoral and cellular immune response. The mRNA technology is transcribed *in vitro* and delivered to cells via lipid nanoparticles (LNP) [[136](#ref-HCImhzy8)]. They are recognized by ribosomes *in vivo* and then translated and modified into functional proteins [[8](#ref-K0Ltu31S)]. The resulting intracellular viral proteins are displayed on surface MHC proteins, provoking a strong CD8+ T cell response as well as a CD4+ T cell and B cell-associated antibody responses [[8](#ref-K0Ltu31S)]. Naturally, mRNA is not very stable and can degrade quickly in the extracellular environment or the cytoplasm. The LNP covering protects the mRNA from enzymatic degradation outside of the cell [[137](#ref-zNKWlCwE)]. Codon optimization to prevent secondary structure formation and modifications of the poly-A tail as well as the 5’ untranslated region to promote ribosomal complex binding can increase mRNA expression in cells. Furthermore, purifying out double-stranded RNA and immature RNA with FPLC (fast performance liquid chromatography) and HPLC (high performance liquid chromatography) technology will improve translation of the mRNA in the cell [[8](#ref-K0Ltu31S),[138](#ref-pRoqjur8)]. Vaccines based on mRNA delivery confer many advantages over traditional viral vectored vaccines and DNA vaccines. In comparison to live attenuated viruses, mRNA vaccines are non-infectious and can be synthetically produced in an egg-free, cell-free environment, thereby reducing the risk of a detrimental immune response in the host [[141](#ref-wYZ6qJMu)]. Unlike DNA vaccines, mRNA technologies are naturally degradable and non-integrating, and they do not need to cross the nuclear membrane in addition to the plasma membrane for their effects to be seen [[8](#ref-K0Ltu31S)]. Furthermore, mRNA vaccines are easily, affordably, and rapidly scalable.

Although mRNA vaccines have been developed for therapeutic and prophylactic purposes, none have previously been licensed or commercialized. Nevertheless, they have shown promise in animal models and preliminary clinical trials for several indications, including rabies, coronavirus, influenza, and cytomegalovirus [[142](#ref-3EUiWZdN)]. Preclinical data previously identified effective antibody generation against full-length FPLC-purified influenza hemagglutinin stalk-encoding mRNA in mice, rabbits, and ferrets [[143](#ref-6wZy2mn8)]. Similar immunological responses for mRNA vaccines were observed in humans in Phase I and II clinical trials operated by the pharmaceutical-development companies Curevac and Moderna for rabies, flu, and zika [[138](#ref-pRoqjur8)]. Positively charged bilayer LNPs carrying the mRNA attract negatively charged cell membranes, endocytose into the cytoplasm [[137](#ref-zNKWlCwE)], and facilitate endosomal escape. LNPs can be coated with modalities recognized and engulfed by specific cell types, and LNPs that are 150 nm or less effectively enter into lymphatic vessels [[137](#ref-zNKWlCwE),[144](#ref-Djz8x39x)]. Therefore, this technology holds great potential for targeted delivery of modified mRNA.

There are three types of RNA vaccines: non-replicating, *in vivo* self-replicating, and *in vitro* dendritic cell non-replicating [[139](#ref-1EM5nGaYd)]. Non-replicating mRNA vaccines consist of a simple open reading frame (ORF) for the viral antigen flanked by the 5’ UTR and 3’ poly-A tail. *In vivo* self-replicating vaccines encode a modified viral genome derived from single-stranded, positive sense RNA alphaviruses [[8](#ref-K0Ltu31S),[138](#ref-pRoqjur8)]. The RNA genome encodes the viral antigen along with proteins of the genome replication machinery, including an RNA polymerase. Structural proteins required for viral assembly are not included in the engineered genome [[8](#ref-K0Ltu31S)]. Self-replicating vaccines produce more viral antigens over a longer period of time, thereby evoking a more robust immune response [[139](#ref-1EM5nGaYd)]. Finally, *in vitro* dendritic cell non-replicating RNA vaccines limit transfection to dendritic cells. Dendritic cells are potent antigen-presenting immune cells that easily take up mRNA and present fragments of the translated peptide on their MHC proteins, which can then interact with T cell receptors. Ultimately, primed T follicular helper cells can stimulate germinal center B cells that also present the viral antigen to produce antibodies against the virus [[140](#ref-3LMMW7F0)]. These cells are isolated from the patient, grown and transfected *ex vivo*, and reintroduced to the patient [[12](#ref-ENBWnhAh)].

Given the potential for this technology to be quickly adapted for a new pathogen, it has held significant interest for the treatment of COVID-19. In the vaccines developed under this approach, the spike protein, which is immunogenic [[145](#ref-5x25saIz)], can be furnished to the immune system in order to train its response. The vaccine candidates developed against SARS-CoV-2 using mRNA vectors utilize similar principles and technologies, although there are slight differences in implementation among candidates such as the formulation of the platform and the specific components of the spike protein encapsulated (e.g., the full Spike protein vs. the RBD alone) [[154](#ref-suRY1e0N)]. The results of the interim analyses of two mRNA vaccine candidates became available at the end of 2020 and provided strong support for this emerging approach to vaccination. Below we describe the results available as of February 2021 for two such candidates, mRNA-1273 produced by ModernaTX and BNT162b2 produced by Pfizer, Inc. and BioNTech.

### 1.1.1 ModernaTX mRNA Vaccine

ModernaTX’s mRNA-1273 vaccine was the first COVID-19 vaccine to enter a phase I clinical trial in the United States. In this trial, Moderna spearheaded an investigation on the immunogenicity and reactogenicity of mRNA-1273, a conventional lipid nanoparticle encapsulated RNA encoding a full-length prefusion stabilized S protein for SARS-CoV-2 [[149](#ref-Biu1CQeQ)]. An initial report described the results of enrolling forty-five participants who were administered intramuscular injections of mRNA-1273 in their deltoid muscle on day 1 and day 29, with the goal of following patients for the next twelve months [[24](#ref-wiGjCZC8)]. Healthy males and non-pregnant females aged 18-55 years were recruited for this study and divided into three groups receiving 25, 100, or 250 micrograms (μg) of mRNA-1273. IgG ELISA assays on patient serology samples were used to examine the immunogenicity of the vaccine [[149](#ref-Biu1CQeQ)]. Binding antibodies were observed at two weeks after the first dose at all concentrations. At the time point one week after the second dose was administered on day 29, the pseudotyped lentivirus reporter single-round-of-infection neutralization assay (PsVNA), which was used to assess neutralizing activity, reached a median level similar to the median observed in convalescent plasma samples. Participants reported mild and moderate systemic adverse events after the day 1 injection, and one severe local event was observed in each of the two highest dose levels. The second injection led to severe systemic adverse events for three of the participants at the highest dose levels, with one participant in the group being evaluated at an urgent care center on the day after the second dose. The reported localized adverse events from the second dose were similar to those from the first.

Several months later, a press release from ModernaTX described the results of the first interim analysis of the vaccine [[155](#ref-IMmoqofb)]. On November 16, 2020, a report was released describing the initial results from Phase III testing, corresponding to the first 95 cases of COVID-19 in the 30,000 enrolled participants [[155](#ref-IMmoqofb)], with additional data released to the FDA on December 17, 2020 [[156](#ref-QEdBZMLe)]. These results were subsequently published in a peer-reviewed journal (*The New England Journal of Medicine*) on December 30, 2020 [[150](#ref-ZYxoabEm)]. The first group of 30,420 study participants were randomized to receive the vaccine or a placebo at a ratio of 1:1 [[150](#ref-ZYxoabEm)]. Administration occurred at 99 sites within the United States in two sessions, spaced 28 days apart [[150](#ref-ZYxoabEm),[157](#ref-16kGLLlT8)]. Patients reporting COVID-19 symptoms upon follow-up were tested for SARS-CoV-2 using a nasopharyngeal swab that was evaluated with RT-PCR [[157](#ref-16kGLLlT8)]. The initial preliminary analysis reported the results of the cases observed up until a cut-off date of November 11, 2020. Of these first 95 cases reported, 90 occurred in participants receiving the placebo compared to 5 cases in the group receiving the vaccine [[155](#ref-IMmoqofb)]. These results suggested the vaccine is 94.5% effective in preventing COVID-19. Additionally, eleven severe cases of COVID-19 were observed, and all eleven occurred in participants receiving the placebo. The publication reported the results through an extended cut-off date of November 21, 2020, corresponding to 196 cases [[150](#ref-ZYxoabEm)]. Of these, 11 occurred in the vaccine group and 185 in the placebo group, corresponding to an efficacy of 94.1%. Once again, all of the severe cases of COVID-19 observed (n=30) occurred in the placebo group, including one death. Thus, as more cases are reported, the efficacy of the vaccine has remained above 90%, and no cases of severe COVID-19 have yet been reported in participants receiving the vaccine.

These findings suggest the possibility that the vaccine might bolster immune defenses even for subjects who do still develop a SARS-CoV-2 infection. The study was designed with an explicit goal of including individuals at high risk for COVID-19, including older adults, people with underlying health conditions, and people of color [[158](#ref-vkczroFC)]. The Phase III trial population was comprised by approximately 25.3% adults over age 65 in the initial report and 24.8% in the publication [[157](#ref-16kGLLlT8)]. Among the cases reported by both interim analyses, 16-17% occurred in older adults [[150](#ref-ZYxoabEm),[155](#ref-IMmoqofb)].. Additionally, approximately 10% of participants identified a Black or African-American background and 20% identified Hispanic or Latino ethnicity [[150](#ref-ZYxoabEm),[157](#ref-16kGLLlT8)]. Among the first 95 cases, 12.6% occurred in participants identifying a Hispanic or Latino background and 4% in participants reporting a Black or African-American background [[155](#ref-IMmoqofb)]; in the publication, they indicated only that 41 of the cases reported in the placebo group and 1 case in the treatment group occurred in “communities of color”, corresponding to 21.4% of all cases [[150](#ref-ZYxoabEm)]. While the sample size in both analyses is small relative to the study population of over 30,000, these results suggest that the vaccine is likely to be effective in people from a variety of backgrounds. By all indications, this vaccine is likely to be highly useful in mitigating the damage of SARS-CoV-2.

In-depth safety data was released by ModernaTX as part of their application for an EUA from the FDA and summarized in the associated publication [[150](#ref-ZYxoabEm),[157](#ref-16kGLLlT8)]. Because the detail provided in the report is greater than that provided in the publication, here we emphasize the results observed at the time of the first analysis. Overall, a large percentage of participants reported adverse effects when solicited, and these reports were higher in the vaccine group than in the placebo group (94.5% versus 59.5%, respectively, at the time of the initial analysis) [[157](#ref-16kGLLlT8)]. Some of these events met the criteria for grade 3 (local or systemic) or grade 4 (systemic only) toxicity [[157](#ref-16kGLLlT8)], but most were grade 1 or grade 2 and lasted 2-3 days [[150](#ref-ZYxoabEm)]. The most common local adverse reaction was pain at the injection site, reported by 83.7% of participants receiving the first dose of the vaccine and 88.4% upon receiving the second dose, compared to 19.8% and 19.8% and 17.0%, respectively, of patients in the placebo condition [[157](#ref-16kGLLlT8)]. Fewer than 5% of vaccine recipients reported grade 3 pain at either administration. Other frequent local reactions included erythema, swelling, and lymphadenopathy [[157](#ref-16kGLLlT8)]. For systemic adverse reactions, fatigue was the most common [[157](#ref-16kGLLlT8)]. Among participants receiving either dose of the vaccine, 68.5% reported fatigue compared to 36.1% participants receiving the placebo [[157](#ref-16kGLLlT8)]. The level of fatigue experienced was usually fairly mild, with only 9.6% and 1.3% of participants in the vaccine and placebo conditions, respectively, reporting grade 3 fatigue [[157](#ref-16kGLLlT8)], which corresponds to significant interference with daily activity [[159](#ref-oJWLuU0h)]. Based on the results of the report, an EUA was issued on December 18, 2020 to allow distribution of this vaccine in the United States [[152](#ref-13Ou1UUAd)], and it was shortly followed by an Interim Order authorizing distribution of the vaccine in Canada [[160](#ref-HwoGQ6DD)] and a conditional marketing authorization by the European Medicines Agency to facilitate distribution in the European Union [[161](#ref-4hVgIXyi)].

### 1.1.2 Pfizer/BioNTech BNT162b2

ModernaTX was, in fact, the second company to release news of a successful interim analysis of an mRNA vaccine and receive an EUA. The first report came from Pfizer and BioNTech’s mRNA vaccine BNT162b2 on November 9, 2020 [[162](#ref-16hlR7Xgi)], and a preliminary report was published in the *New England Journal of Medicine* one month later [[148](#ref-CWlYjjIV)]. The vaccine candidate is contains the full prefusion stabilized, membrane-anchored SARS-CoV-2 spike protein in a vaccine formulation based on modified mRNA (modRNA) technology [[146](#ref-1CsCQi9wT),[147](#ref-10VyxCgQU)]. This vaccine candidate should not be confused with a similar candidate from Pfizer/BioNTech, BNT162b1, that delivered only the RBD of the spike protein [[163](#ref-dlqAfQ7t),[164](#ref-T3BkYtz2)], which was not advanced to a stage III trial because of the improved reactogenicity/immunogenicity profile of BNT162b2 [[165](#ref-MD2K7MYB)].

During the Phase III trial of BNT162b2, 43,538 participants were enrolled 1:1 in the placebo and the vaccine candidate and received two 30-μg doses 21 days apart [[148](#ref-CWlYjjIV)]. Of these enrolled participants, 21,720 received BNT162b2 and 21,728 received a placebo [[148](#ref-CWlYjjIV)]. Recruitment occurred at 135 sites across six countries: Argentina, Brazil, Germany, South Africa, Turkey, and the United States. An initial press release described the first 94 cases, which were consistent with 90% efficacy of the vaccine at 7 days following the second dose [[162](#ref-16hlR7Xgi)]. The release of the full trial information covered a longer period and analyzed the first 170 cases occurring at least 7 days after the second dose, 8 of which occurred in patients who had received BNT162b2. The press release characterized the study population as diverse, reporting that 42% of the participants worldwide came from non-white backgrounds, including 10% Black and 26% Hispanic or Latino [[166](#ref-EMWkcH5x)]. Within the United States, 10% and 13% of participants, respectively, identified themselves as having Black or Hispanic/Latino backgrounds [[166](#ref-EMWkcH5x)]. Additionally, 41% of participants worldwide were 56 years of age or older [[166](#ref-EMWkcH5x)], and they reported that the efficacy of the vaccine in adults over 65 was 94% [[167](#ref-Ufs4s7hG)]. The primary efficacy analysis of the Phase III study was concluded on November 18, 2020 [[167](#ref-Ufs4s7hG)], and the final results indicted 94.6% efficacy of the vaccine [[148](#ref-CWlYjjIV)].

The safety profile of the vaccine was also assessed [[148](#ref-CWlYjjIV)]. A subset of patients were followed for reactogenicity using electronic diaries, with the data collected from these 8,183 participants comprising the solicited safety events analyzed. Much like those who received the ModernaTX vaccine candidate, a large proportion of participants reported experiencing site injection pain within 7 days of vaccination. While percentages are broken down by age group in the publication, these proportions correspond to approximately 78% and 73% of all participants after the first and second doses, respectively, overall. Only a small percentage of these events (less than 1%) were rated as serious, with the rest being mild or moderate, and none reached grade 4. Some participants also reported redness or swelling, and the publication indicates that in most cases, such events resolved within 1 to 2 days. Participants also experienced systemic effects, including fever (in most cases lower than 38.9°C and more common after dose 2), fatigue (25-50% of participants depending on age group and dose), headache (25-50% of participants depending on age group and dose), chills, and muscle or joint pain; more rarely, patients could experience gastrointestinal effects such as vomiting or diarrhea. As with the local events, these events were almost always grade I or II. While some events were reported by the placebo groups, these events were much rarer than in the treatment group even though compliance was similar. Based on the efficacy and safety information released, the vaccine was approved in early December by the United Kingdom’s Medicines and Healthcare Products Regulatory Agency with administration outside of a clinical trial beginning on December 8, 2020 [[168](#ref-31rsgfCB),[169](#ref-fhw7l8VO)]. As of December 11, 2020, the United States FDA approved this vaccine under an emergency use authorization [[151](#ref-cAaN4Te0)].

## 1.2 Viral Vector Vaccines

### 1.2.1 ChAdOx1 nCoV-19 (AstraZeneca)

As discussed above, prior analyses of viral vector vaccines against hCoV had indicated that this approach showed potential for inducing an immune response, but little information was available about the effect on real-world immunity. In the first phase of development, a candidate ChAdOx1 nCoV-19 was evaluated through the immune challenge of two animal models, mice and rhesus macaques [[104](#ref-1037p4Gvs)]. Animals in the treatment condition were observed to develop neutralizing antibodies specific to SARS-CoV-2 (both macaques and mice) and to show reduced clinical scores when exposed to SARS-CoV-2 (macaques) [[104](#ref-1037p4Gvs)]. Next, a phase I/II trial was undertaken using a single-blind, randomized controlled design [[105](#ref-2bBVSpM)]. ChAdOx1 nCoV-19 and a control, the meningococcal conjugate vaccine MenACWY, were administered intramuscularly to adults ages 18 to 55 at five sites within the United Kingdom (U.K.) at a 1:1 ratio (n=543 and n=534, respectively). All but ten participants received a single dose; this small group received a booster 28 days after their first dose of ChAdOx1 nCoV-19. Commonly reported local adverse reactions included mild-to-moderate pain and tenderness at the injection site over the course of seven days, while the most common systemic adverse reactions were fatigue and headache; some patients reported severe adverse systemic effects. The study also reported that many common reactions could be reduced through the administration of paracetamol (acetaminophen), and paracetamol was not found to reduce immunogenicity. Patients receiving the ChAdOx1 nCoV-19 vaccine developed antibodies to the SARS-CoV-2 spike protein that peaked by day 28, with these levels remaining stable until a second observation at day 56 except in the ten patients who received a booster dose at day 28, in whom they increased by day 56. Analysis of serum indicated that participants developed antibodies to both S and the RBD, and that 100% of them achieved neutralizing titers by day 28. By day 35, the neutralization titers of vaccinated patients was comparable to that observed with plasma from convalescents. This initial study therefore suggested that the vaccine was likely to confer protection against SARS-CoV-2, although analysis of its efficacy in preventing COVID-19 was not reported.

In December 2020, preliminary results of the phase III trial were released detailing randomized control trials conducted in the U.K., Brazil, and South Africa between April and November 2020 [[19](#ref-Vnbw9o3T)]. These trials again compared ChAdOx1 nCoV-19 to a control, but the design of each study varied. For example, in South Africa, the trial was double-blinded, whereas in the U.K. and Brazil it was single-blinded, and one of the two trials carried out in the U.K. examined two dosing regimens (low dose or standard dose, both followed by standard dose). Some of the trials used MenACWY as a control, while others used saline. Data was pooled across countries for analysis. The primary outcome assessed was symptomatic, laboratory-confirmed COVID-19. There were 131 cases observed among the 11,636 participants eligible for the primary efficacy analysis, corresponding to an overall efficacy of 70.4% (30 out of 5807 in the vaccine arm and 101 out of 5829 in the control arm); the 95.8% CI was reported as 54.8 to 80.6. However, a higher efficacy was reported in the subgroup of patients who received a low-dose followed by a standard dose (90.0%, 95% CI 67.4 to 97·0). A total of ten cases of severe COVID-19 resulting in hospitalization were observed among trial participants, and all of these occurred in patients in the control arm of the study. In line with the previously reported safety profiling for this vaccine, serious adverse events were reported to be comparable across the two arms of the study, with only three events identified as potentially associated with the vaccine itself. The U.K. Medicines and Healthcare Products Regulatory Agency (MHRA) approved ChAdOx1 nCoV-19 for emergency use on December 30, 2020 [[106](#ref-1A7PjhDDR)]. Additional data about the efficacy of this vaccine became available in a preprint released on March 2, 2021 [[170](#ref-eV6UplSu)]. This report provided data describing the efficacy of ChAdOx1 nCoV-19, along with Pfizer/BioNTech’s BNT162b2, in the U.K. between December 8, 2020 and February 19, 2021 and specifically sought to evaluate the efficacy of the vaccine in the presence of a potentially more contagious variant of concern, B.1.1.7. All participants in this study were age 70 or older and the efficacy was estimated to increase from 60% at 28 days after vaccination to 73% at 35 days after vaccination, although the standard error also increased over this time. Therefore, preliminary results suggest that in a number of samples, this vaccine confers a high level of protection against SARS-CoV-2.

### 1.2.2 Sputnik-V (Gam-COVID-Vac and Gam-COVID-Vac-Lyo)

The vaccine Gam-COVID-Vac, nicknamed Sputnik V in reference to the space race and “V for vaccine”, was developed by the Gamaleya National Center of Epidemiology and Microbiology in Moscow. Gamaleya is an organization with prior experience using the adenovirus platform for the development of vaccines for *Middle East respiratory syndrome-related coronavirus* and Ebola virus, although neither of the previous vaccines were internationally licensed [[100](#ref-UCI0TCHy)]. The development of Sputnik V was financed by the Russian Direct Investment Fund (RDIF) [[107](#ref-3KMxmQhV),[171](#ref-SxiGicKs)]. Sputnik V is a replication-deficient recombinant adenovirus (rAd) vaccine that combines two adenovirus vectors, rAd26-S and rAd5-S, that express the full-length SARS-CoV-2 spike glycoprotein. These vectors are intramuscularly administered individually using two separate vaccines in a prime-boost regimen. The rAd26-S is administered first, followed by rAd5-S 21 days later. Both vaccines deliver 1011 viral particles per dose. This approach is designed to overcome any potential pre-existing immunity to adenovirus in the population [[172](#ref-sRAZYY9C)], as some individuals may possess immunity to Ad5 [[173](#ref-8jwp261S)]. Sputnik V is the only recombinant adenovirus vaccine to utilize two vectors. Other vaccines, such as the Oxford-AstraZeneca vaccine, utilize the chimpanzee adenovirus vector (ChAdOx1 nCoV-19) for both doses [[174](#ref-LZ8AtMnD)]. The Sputnik V vaccines are available in both a lyophilized (Gam-COVID-Vac-Lyo) and frozen form (Gam-COVID-Vac), which are stored at 2-8°C and -18°C respectively [[108](#ref-PNZEiId1)]. The lyophilized vaccine is convenient for distribution and storage, particularly to remote or disadvantaged areas [[175](#ref-3KBugyZN)].

In the race to develop vaccines against SARS-CoV-2, President Vladimir Putin of Russia announced the approval of the Sputnik V vaccines on August 11th, 2020 in the absence of clinical evidence [[107](#ref-3KMxmQhV)]. Consequently, many international scientific agencies and public health bodies expressed concern that due diligence to the clinical trial process was subverted for the sake of expediency, leading many to question the safety and efficacy of Sputnik V [[107](#ref-3KMxmQhV),[176](#ref-15DiM98Ae),[177](#ref-x4aIj5Fr)]. Despite regulatory, safety, and efficacy concerns, pre-orders for 1 billion doses of the Sputnik V were reported within days of the vaccine’s approval in Russia [[107](#ref-3KMxmQhV)]. Almost a month later, the phase I/II trial data was published [[108](#ref-PNZEiId1)].

In the phase I/II trial study conducted between late June and early August 2020, 76 participants (18-60 years old) were split into two groups of 38 participants, which were non-randomized in two hospitals in Russia. In phase I, 9 patients received rAd26 and 9 patients received rAd5-S to assess safety over 28 days. In phase II, at least 5 days after the completion of phase I, 20 patients received a prime-boost vaccination of rAd26-S on day 0 and rAd5-S on day 2, which was administered intramuscularly. The phase I/II trial reported that both vaccines were deemed safe and well tolerated. The most common adverse events reported were mild, such as pain at the injection site (58%), hypothermia (50%), headaches (42%), fatigue (28%), and joint and muscle pain (24%). Seroconversion was observed in all participants three weeks post the second vaccination (day 42), and all participants produced antibodies to the SARS-CoV-2 glycoprotein. RBD-specific IgG levels were high in both the frozen and lyophilized versions of the vaccine (14,703 and 11,143 respectively), indicating a sufficient immune response to both. Three weeks post the second vaccination, the virus-neutralizing geometric mean antibody titers were 49.25 and 45.95 from the frozen and lyophilized vaccines, respectively. At 28 days, median cell proliferation of 1.3% CD4+ and 1.1% CD8+ were reported for the lyophilized vaccine and 2.5% CD4+ and 1.3% CD8+ for the vaccine stored frozen. These results indicated that both forms of Sputnik V appeared to be safe and induce a humoral and cellular response in human subjects [[108](#ref-PNZEiId1)], which may be robust enough to persist and not wane rapidly [[172](#ref-sRAZYY9C)].

A press release on November 11th, 2020 indicated positive results from an interim analysis of the phase III Sputnik V trials, which reported 92% efficacy in 16,000 volunteers [[178](#ref-JSzDvnk6)]. However, this release came only two days after both Pfizer and BioNTech reported that their vaccines had an efficacy over 90%, which led to significant skepticism of the Russian findings for a myriad of reasons including the lack of a published protocol and the “reckless” approval of the vaccine in Russia months prior to the publication of the interim results of the phase III trial [[178](#ref-JSzDvnk6),[179](#ref-Yzz3rwqk)]. In February 2021, the interim results of the phase III randomized, double-blind, placebo-controlled trial were eventually published in *The Lancet* [[109](#ref-gLAIyAHm)]. The participants were randomly assigned to receive either a 0.5 mL/dose of vaccine or placebo, which was comprised of the vaccine buffer composition, that was delivered intramuscularly using the same prime-boost regimen as in the phase I/II trials. From September 7th to Nov 24th, 19,866 participants completed the trial. Of the 14,964 participants who received the vaccine, 16 (0.1%) were confirmed to have COVID-19, whereas 62 of the 4,902 participants (1.3%) in the placebo group were confirmed to have COVID-19. Of these participants, no moderate or severe cases of COVID-19 were reported in the vaccine group, juxtaposed with 20 in the placebo group. However, only symptomatic individuals were confirmed for SARS-CoV-2 infection in this trial. Therefore, asymptomatic infections were not detected, thus potentially inflating the efficacy estimate. Overall, a vaccine efficacy of 91.6% (95% CI 85.6-95.2) was reported, where an efficacy of 91.8% was reported for those over 60 years old and 92.7% for those who were 51-60 years old. Indeed, 14 days after the first dose, 87.6% efficacy was achieved and the immunity required to prevent disease occurred within 18 days of vaccination. Based on these results, scientists are investigating the potential for a single dose regimen of the rAd26-S sputnik V vaccine [[180](#ref-wCTVieA3)]. By the end of the trial, 7,485 participants reported adverse events, of which 94% were grade I. Of the 68 participants who experienced serious adverse events during the trial, 45 from the vaccine group and 23 from the placebo groups, none were reported to be associated with the vaccination. Likewise, 4 deaths occurred during the trial period that were not related to the vaccine [[109](#ref-gLAIyAHm)]. The interim findings of the phase III trial indicate that the Sputnik V vaccine regimen appears to be safe with 91.6% efficacy. Gamaleya had intended to reach a total of 40,000 participants for the completion of their phase III trial. However, the trial has stopped enrolling participants and the numbers have been cut to 31,000 as many individuals in the placebo group dropped out of the study to obtain the vaccine [[181](#ref-15qYogj0H)]. Indeed, other trials involving Sputnik V are currently underway in Belarus, India, the United Arab Emirates, and Venezuela [[182](#ref-vrzaW9Gb)/].

Preliminary results of a trial of Argentinian healthcare workers in Buenos Aires who were vaccinated with the Sputnik V rAd26-R vector-based vaccine seems to support the short term safety of the first vaccination [[183](#ref-vTFvCt1w)]. Of the 707 vaccinated healthcare workers, 71.3% of the 96.6% of respondents reported at least one adverse event attributed to the vaccine. Of these individuals, 68% experienced joint and muscle pain, 54% had injection site pain, 11% reported redness and swelling, 40% had a fever, and 5% reported diarrhea. Only 5% of the vaccinated participants experienced serious adverse events that required medical attention, of which one was monitored as an inpatient.

Additionally, an Independent assessment of Sputnik V in a phase II clinical trial in India found the vaccine to be effective, but the data is not yet publicly available [[184](#ref-jv875POj)]. On December 21st, 2020, Gamaleya, AstraZeneca, R-Pharm, and the Russian Direct Investment Fund agreed to assess the safety and immunogenicity of the combined use of components of the AstraZeneca and University of Oxford AZD1222 (ChAdOx1) vaccine and the rAd26-S component of the Sputnik V vaccine in clinical trials [[185](#ref-150qGOMi9)/]. This agreement hopes to establish scientific and business relations between the entities with an aim to co-develop a vaccine providing long-term immunization. The trial, which will begin enrollment soon, will include 100 participants in a phase II open-label study and is hoped to be complete within 6 months. Participants will first receive an intramuscular dose of AZD1222 on day 1, followed by a dose of rAd26 on day 29. Participants will be monitored from day 1 for 180 days in total. The primary outcomes measured will include incidence of serious adverse events post first dose until the end of the study. Secondary outcome measures will include incidence of local and systemic adverse events 7 days post each dose, a time course of antibody responses for the Spike protein and the presence of anti-SARS-CoV-2 neutralizing antibodies [[186](#ref-1G2ROkAsZ)].

Overall, there is hesitancy surrounding the management of the Sputnik V vaccine approval process and concerns over whether the efficacy data may be inflated due to a lack of asymptomatic testing within the trial. However, the interim results of the phase III study were promising and further trials are underway, which will likely shed light on the overall efficacy and safety of the Sputnik V vaccine regimen. There may be some advantage to the Sputnik V approach including the favorable storage conditions afforded by choice between a frozen and lyophilized vaccine. Furthermore, the producers of Gam-COVID-Vac state that they can produce the vaccine at a cost of less than $10 per dose or less than $20 per patient [[187](#ref-AfkC38Sh)].

### 1.2.3 Janssen’s JNJ-78436735

The Johnson & Johnson (J&J) vaccine developed by Janssen Pharmaceuticals, Inc., a subsidiary of J&J, was conducted in collaboration with and funded by “Operation Warp Speed” [[115](#ref-D3Px25HN),[116](#ref-57BTbcko)]. The vaccine candidate JNJ-78436735, formerly known as Ad26.COV2-S, is a monovalent vaccine that is composed of a replication-deficient adenovirus serotype 26 (Ad26) vector expressing the stabilized pre-fusion S protein of SARS-CoV-2 [[117](#ref-pWf2T8J8),[118](#ref-10UC562ga)]. The vaccine was developed using Janssen’s AdVac® and PER.C6 platforms that were previously utilized to develop the European Commission-approved Ebola vaccine (Ad26 ZEBOV and MVN-BN-Filo) and their Zika, respiratory syncytial (RSV), and HIV investigational vaccine candidates [[188](#ref-10uLoe1rR)].

The development of a single-dose vaccine was desirable by J&J from the outset, with global deployment being a key priority [[119](#ref-gOOBv1MD)]. Using their AdVac® technology, the vaccine can remain stable for up to two years between -15℃ and -25℃ and at least three months at 2-8℃ [[188](#ref-10uLoe1rR)]. This allows the vaccine to be distributed easily without the requirement for very low temperature storage, unlike many of the other COVID-19 vaccine candidates. J&J screened numerous potential vaccine candidates *in vitro* and in animal models using varying different designs of the S protein, heterologous signal peptides, and prefusion-stabilizing substitutions [[118](#ref-10UC562ga)]. A select few candidates were further investigated as a single dose regimen in Syrian golden hamsters, a single dose regimen in rhesus macaques, and a single- and two-dose regimen in both adult and aged rhesus macaques [[118](#ref-10UC562ga),[119](#ref-gOOBv1MD),[120](#ref-HmMIiIv2),[121](#ref-EpOXYGt4)]. From these studies, the JNJ-78436735 candidate was selected for its favorable immunogenicity profile and ease of manufacturability [[118](#ref-10UC562ga),[119](#ref-gOOBv1MD),[120](#ref-HmMIiIv2),[121](#ref-EpOXYGt4)]. A SARS-CoV-2 challenge study in rhesus macaques showed that vaccine doses as low as 2 x 109 viral particles/mL was sufficient to induce strong protection in bronchoalveolar lavage but that doses higher than 1.125 x 1010 were required to close achieve close to complete protection in nasal swabs [[189](#ref-lVoienSE)]. Indeed, six months post-immunization, levels of S-binding and neutralizing antibodies in rhesus macaques indicated that the JNJ-78436735 vaccine conferred durable protection against SARS-CoV-2 [[122](#ref-HGVDPMLm)].

Following selection of the JNJ-78436735 vaccine, J&J began phase I/IIa trials. The interim phase I/IIa data was placed on the *medRxiv* preprint server on September 25th, 2020 [[190](#ref-14g52GtO3)] and was later published in the *New England Journal of Medicine* on January 13th, 2021 [[117](#ref-pWf2T8J8)]. The phase I/IIa multi-center, randomized, placebo-controlled trial enrolled 402 healthy participants between 18-55 years old and a further 403 healthy older participants ≥ 65 years old [[117](#ref-pWf2T8J8)]. Patients were administered either a placebo, a low dose (5 x 1010 viral particles per mL), or a high dose (1 X 1011 viral particles per mL) intramuscularly as part of either a single- or two-dose regimen. All patients received injections 56 days apart, but participants in the single-dose condition received the placebo at the second appointment. Those who received only one dose of either vaccine received a placebo dose at their second vaccination visit. A comparison of the single versus double dose regimen has yet to be published. The primary endpoints of both the trial were safety and reactogenicity of each dose. Fatigue, headache, myalgia, and pain at the injection site were the most frequent solicited adverse events reported by participants. Although less common, particularly for those in the elderly cohort and those on the low dose regimen, the most frequent systemic adverse effect was fever. Overall, immunization was well tolerated, particularly at the lower dose concentration. In terms of reactogenicity, over 90% of those who received either the low or high dose demonstrated seroconversion in a neutralization assay using wild-type SARS-CoV-2, 29 days after immunization [[117](#ref-pWf2T8J8)]. Neutralizing geometric mean ratio of antibody titers (GMT) between 224-354 were detected regardless of age. By day 57, 100% of the 18-55 year old participants had neutralizing GMT (288-488), which remained stable until day 71. In the ≥ 65 years old cohort, the incidence of seroconversion for the low- and high-dose was 96% and 88% respectively by day 29.

GMTs for the low and high doses were slightly lower for participants ≥ 65 years old (196 and 127 respectively), potentially indicating slightly lower immunogenicity. Seroconversion of the S antibodies was detected in 99% of individuals between 18-55 years old for the low and high doses (GMTs 528 and 695 respectively), with similar findings reported for the ≥ 65 years old. Indeed, both dose concentrations also induced robust Th1 cytokine-producing S-specific CD4+ T cells and CD8+ T cell responses in both age groups. The findings of the phase I/IIa study supported further investigation of a single immunization using the low dose vaccine. Therefore, 25 patients were enrolled for a second randomized double-blind, placebo-controlled phase 1 clinical trial currently being conducted in Boston, Massachusetts for 2 years [[191](#ref-1CBMCD5I2)]. Participants received either a single dose followed by a placebo, or a double dose of either a low dose (5 x 1010 viral particles/mL) or a high dose (1 x 1011 viral particles/mL) vaccine administered intramuscularly on day 1 or day 57. Placebo-only recipients received a placebo dose on day 1 and 57. Interim analyses conducted on day 71 indicated that binding and neutralizing antibodies developed 8 days after administration in 90% and 25% of vaccine recipients, respectively. Binding and neutralizing antibodies were detected in 100% of vaccine recipients by day 57 after a single dose immunization. Spike-specific antibodies were highly prevalent (GMT 2432 to 5729) as were neutralizing antibodies (GMT 242 to 449) in the vaccinated groups. Indeed, CD4+ and CD8+ T-cell responses were also induced, which may provide additional protection, particularly if antibodies wane or poorly respond to infection [[192](#ref-1GRYnvF01)].

On September 23rd, 2020, J&J launched its phase III trial ENSEMBLE and released the study protocol to the public [[188](#ref-10uLoe1rR),[193](#ref-7n6WEkK8)]. The trial intended to enroll 60,000 volunteers to assess the safety and efficacy of the single vaccine dose versus placebo with primary endpoints of 14 and 28 days post-immunization [[188](#ref-10uLoe1rR)]. The trial was conducted in Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, and the U.S. The trial was paused briefly in October 2020 to investigate a “serious medical event”, but resumed shortly after [[194](#ref-5BTmfe4Y)]. An interim analysis was reported via press release on January 29th, 2021 [[123](#ref-iWMHpTBJ),[124](#ref-1FcpboRMm)]. The interim data included 43,783 participants who accrued 468 symptomatic cases of COVID-19. It was reported that the JNJ-78436735 vaccine was 66% effective across all regions studied for the prevention of moderate to severe COVID-19 28 days post-vaccination in those aged 18 years and older. Notably, JNJ-78436735 was 85% effective for the prevention of laboratory-confirmed severe COVID-19 and 100% protection against COVID-19-related hospitalization and death 28 days post-vaccination across all study sites. Efficacy of the vaccine against severe COVID-19 increased over time, and there were no cases of COVID-19 reported in immunized participants after day 49. The trial also determined that the vaccine candidate has a favorable safety profile as determined by an independent Data and Safety Monitoring Board. The vaccine was well tolerated, consistent with previous vaccines produced using the AdVac® platform. Fever occurred in 9% of vaccine recipients, with grade 3 fever occurring in only 0.2% of recipients. Serious adverse events were reportedly higher in the placebo group than the vaccine group, and no anaphylaxis was reported [[124](#ref-1FcpboRMm)].

At the time the phase III trial was being conducted, several concerning variants, including B.1.1.7 [[195](#ref-m9qtrWft)] and B.1.351 [[125](#ref-sqhvCTIL)], were spreading across the globe. In particular, B.1.351 was first identified in South Africa, which was one of the JNJ-78436735 vaccine trial sites. Therefore, the J&J investigators also analyzed the efficacy of the JNJ-78436735 vaccine associated with their various trial sites to determine any potential risk of reduced efficacy as a result of the novel variants. It was determined that JNJ-78436735 was 72% effective in the U.S., 66% effective in Latin America, and 57% effective in South Africa 28 days post-vaccination. These findings underpin the importance of monitoring for the emergence of novel SARS-CoV-2 variants and determining their effects on vaccine efficacy.

Looking forward, Janssen are also running a phase III randomized, double-blind, placebo-controlled clinical trial, Ensemble 2, which aims to assess the efficacy, safety, and immunogenicity of a two-dose regimen of JNJ-78436735 administered 57 days apart. This trial will enroll 30,000 participants ≥ 18 years old from Belgium, Colombia, France, Germany, Philippines, South Africa, Spain, U.K., and the U.S. [[196](#ref-sx7F1ktj)]. This trial will also include participants with and without comorbidities associated with an increased risk of COVID-19.

### 1.2.4 Overall Status of Viral-Vector Vaccines

The three viral-vector vaccines described above have demonstrated the potential for this technology to facilitate a quick response to an emerging pathogen. However, two of the three vaccines have faced a number of criticisms surrounding the implementation of their clinical trials. <–To Do: Suggestion to move some of the Sputnik controversy here, along with describing the issues with the AstraZeneca trial–>

Additionally, though the vaccines are built using similar principles, there are some differences that might influence their efficacy as SARS-CoV-2 evolves. <–To Do: suggestion to discuss prefusion conformation (J&J) vs not (the other two)–>

## 1.3 Sinovac’s CoronaVac

The CoronaVac vaccine is being developed by Sinovac, a Beijing-based biopharmaceutical company. The vaccine is using an inactivate whole virus with the addition of an aluminum adjuvant [[43](#ref-RGPoDfHS)]. The vaccine is currently in Phase III clinical trials.

Pre-clinical trials were performed using BALB/c mice and rhesus macaques [[46](#ref-14fILrRWg)]. The SARS-CoV-2 strains used in this trial isolated from 11 hospitalized patients (5 from China, 3 from Italy, 1 from the UK, 1 from Spain, 1 from Switzerland). A phylogenetic analysis demonstrated that the strains were representative of the current circulating variants. One of the strains, CN2, from China was used as the inactivated and purified virus while the other 10 strains were used to challenge. The CN2 was grown in Vero cells. An ELISA assay was used to assess the immunogenicity of the vaccine. 10 mice were injected with the vaccine on day 0 and day 7 with varying doses (0, 1.5, 3 or 6 μg), and 10 mice were treated with physiological saline as the control. IgG developed in the serum of all vaccinated mice. Using the same setup, immunogenicity was also assessed in macaques. Four macaques were assigned to each of four groups: treatment with 3 μg at day 0, 7 and 14, treatment with a high dose of 6 μg at day 0, 7 and 14, administration of a placebo vaccine, and administration of only the adjuvant. All vaccinated macaques induced IgGs and neutralizing antibodies. After challenge with SARS-CoV-2 strain CN1, vaccinated macaques were protected compared to control macaques (placebo or adjuvant only) based on histology and viral loads collected from different regions of the lung.

Phase I/II clinical trials were conducted in adults 18-59 years old [[47](#ref-N1txjPtt)] and adults over 60 years old [[45](#ref-Ozya5HP5)] in China. In the case of adults 18-59 years old, a single center, randomized, double-blind, placebo-controlled phase I/II trial was conducted in April 2020. Patients in this study were recruited from the community in Suining County of Jiangsu province, China. For the phase I trial, 144 (of 185 screened) participants were enrolled, with 72 enrolled in the 14-day interval cohort (i.e., treated on day 0 and day 14) and 72 in the 28-day interval cohort. This group of 72 participants was split into 2 blocks for a low-dose (3 μg) and high-dose (6 μg) vaccine. Within each block, participants were randomly assigned vaccination with CoronaVac or placebo (aluminum diluent without the virus) at a 2:1 ratio. Both the vaccine and placebo were prepared in a Good Manufacturing Practice-accredited facility of Sinovac Life Sciences (Beijing, China).

The phase II trial followed the same organization of participants, this time using 300 enrolled participants in the 14-day and another 300 enrolled in the 28-day groups. One change of note was that the vaccine was produced using a highly automated bioreactor (ReadyToProcess WAVE 25, GE, Umeå, Sweden) to increase vaccine production capacity. This change resulted in a higher intact spike protein content. The authors of this study were not aware of this antigen-level difference between the vaccine batches for the phase I/II when the ethical approval for the trials occurred.

To assess adverse responses, participants were asked to record any events up to 7 days post-treatment. The reported adverse events were graded according to the China National Medical Products Administration guidelines. In the phase I trial, the overall incidence of adverse reactions was 29-38% of patients in the 0 to 14 day group and 13-17% in the 0 to 28 day vaccination group. The most common symptom was pain at the injection site, which was reported by 17-21% of patients in the 0 to 14 day cohort and 13% in the 0 to 28 day cohort. Most adverse reactions were mild (grade 1) where patients recovered within 48 hours. A single case of acute hypersensitivity with manifestation of urticaria 48 hours following the first dose of study drug was reported in the 6 μg group Most adverse reactions were mild (grade 1) in severity and participants recovered within 48 hours. There was a single case, from the 6 μg group, of acute hypersensitivity with manifestation of urticaria 48 hours after the first dose. Both the 14-day and 28-day cohorts had a strong neutralizing Ab response. The neutralizing Ab response was measured using a micro cytopathogenic effect assay, which assesses the minimum dilution of neutralizing Ab to be 50% protective against structural changes in host cells in response to viral infection [[153](#ref-1GUVvcQjL)]. Additionally IgG antibody titers against the receptor binding domain were also measured using ELISA.

Another phase I/II study was performed with older patients (older than 60 years) [[45](#ref-Ozya5HP5)]. The study conducted a single-center, randomized, double-blind, placebo-controlled trial. The phase I trial looked at dose escalation using 3 dosages: 1.5, 3 and 6 μg. The mean age of participants was 65.8 years (std = 4.8). Of 95 screened participants, 72 were enrolled. These 72 participants were split into low (3 μg) and high (6 μg) dose groups. Within each group, 24 participants received the treatment and 12 the placebo. A neutralizing antibody response against live SARS-CoV-2 was detected compared to baseline using the same micro cytopathogenic effect assay. This response was similar across the two dose concentrations. Additionally, they did not observe a difference in response between age groups (60–64 years, 65–69 years, and ≥70 years).

In phase II the mean age was 66.6 years (standard deviation = 4.7). 499 participants were screened and 350 were enrolled. 300 were evenly split into 1.5, 3 and 6 μg dose groups, and the remaining 50 were assigned to the placebo group. Again, they found a neutralizing antibody response in phase II. There wasn’t a significant different between the response to 3 μg versus 6 μg, but the response was higher than that to 1.5 μg.

Participants were required to record adverse reaction events within the first 7 days after each dose. The safety results were combined across phage I and II. All adverse reactions were either mild (grade 1) or moderate (grade 2) in severity. The most common symptom was pain at the injection site (9%) and fever (3%). 2% (7 participants) reported severe adverse events (4 from the 1.5 μg group, 1 from the 3 μg group, 2 from the 6 μg group), though these were found to be unrelated to the vaccine.

Overall, the results from the pre-clinical and phase I/II clinical trials are promising. It was also very hopeful to see that the immune response was consistent in older adults (> 60 years). Currently, phase III trials are being conducted in Brazil [[44](#ref-KewHbkLZ)]. This is a randomized, multicenter, endpoint driven, double-blind, placebo-controlled clinical trial. They are expecting 13,060 participants with 11,800 ages 18 to 59 years and 1,260 age 60+. Participants will be health care professionals.

## 1.4 Protein Subunit Vaccines

Compared to the inactivated whole virus vaccines, these protein subunit vaccines isolate a single protein of the virus and use it to stimulate the immune system. These proteins, also referred to as antigens, are usually those located on the surface of the viral particle and are therefore key targets of the immune system. These proteins are typically grown in yeast and then harvested. This vaccine can stimulate antibodies and CD4+ T-cell response [[69](#ref-12eGVhH5I)]. The main advantage of this method is that they are considered very safe because the antigen alone cannot cause an infection; however, the immune response is weaker and an adjuvant is usually needed to boost the response [[70](#ref-mv42t1HV)].

### 1.4.1 Novavax NVX-CoV2373

Novavax-CoV2373 is a protein nanoparticle vaccine candidate against SARS-CoV-2. The vaccine is constructed from a mutated SARS-CoV-2 spike protein in combination with a specialized adjuvant to elicit an immune response against SARS-CoV-2. The spike protein is recombinantly expressed in Sf9 insect cells [[71](#ref-Qk33ZrIC)], which have previously been used for several other FDA-approved protein therapeutics [[72](#ref-RQR2sOmx)]. The expressed spike protein contains mutations in the furin cleavage site (682-RRAR-685 to 682-QQAQ-685) to avoid cleavage of the spike protein as well as two proline substitutions (K986P and V987P) to improve thermostability [[71](#ref-Qk33ZrIC)]. The improved stability caused by the proline substitutions is particularly critical to facilitating global distribution, particularly to regions where local refrigerator/freezer capacities are limited. Importantly, these amino acid substitutions did not affect the ability of the spike protein to bind the hACE2 receptor (the target receptor of SARS-CoV-2 spike protein). The Novavax-CoV2373 vaccine candidate uses a proprietary, saponin-based Matrix-MTM adjuvant that contains two different 40nm-sized particles formed by formulating purified saponin with cholesterol and phospholipids [[197](#ref-1F52Wz7mx)]. In preclinical models, the use of the Matrix-M adjuvant potentiated the cellular and humoral immune responses to influenza vaccines [[197](#ref-1F52Wz7mx),[198](#ref-scwOT7dw),[199](#ref-aD5iMC0Q),[200](#ref-twmXSpc9)]. Importantly, Matrix-M adjuvant-containing vaccines have shown acceptable safety profiles in human clinical trials [[201](#ref-jVCL0201)].

In preclinical mouse models, Novavax-CoV2373 elicited high anti-spike IgG titers 21-28 days post-vaccination that could neutralize the SARS-CoV-2 virus and protect the animals against virus challenge [[71](#ref-Qk33ZrIC)]. Antibody titers were significantly elevated in groups receiving the vaccine with the Matrix-M adjuvant compared to the groups without adjuvant. Novavax-CoV2373 was able to induce a multifunctional CD4/CD8 T-cell responses and generate high frequencies of follicular helper T-cells and B-cell germinal centers after vaccination. These findings were subsequently evaluated in a baboon primate model, in which Novavax-CoV2373 also elicited high antibody titers against the SARS-CoV-2 spike protein, as well as an antigen specific T-cell response. Based on this data Novavax initiated a Phase 1/2 clinical trial to evaluate the safety and immunogenicity of Novavax-CoV2373 with Matrix-M [[73](#ref-dMLXxGAI),[202](#ref-Nq0cimEs)].

The phase I/II trial was a randomized, placebo-controlled study with 131 healthy adult participants in 5 treatment arms [[73](#ref-dMLXxGAI)]. Participants that received the recombinant SARS-CoV-2 vaccine with or without the Matrix-M adjuvant got two injections, 21 days apart. Primary outcomes that were assessed include reactogenicity, lab-values (serum chemistry and hematology), and anti-spike IgG levels. Secondary outcomes measured included virus neutralization, T-cell responses, and unsolicited adverse events. The authors reported that no serious treatment-related adverse events occurred in any of the treatment arms. Reactogenicity was mostly absent and of short duration. The two-dose vaccine regimen induced anti-spike IgG levels and neutralizing antibody-titers exceeding those in the convalescent plasma of symptomatic patients. In line with the preclinical studies, the use of Matrix-M adjuvant further increased anti-spike immunoglobulin levels and induced a Th1 response. The outcomes of this trial suggest that Novavax-CoV2373 has an acceptable safety profile and is able to induce a strong immune response with high neutralizing antibody titers. The phase II component of this phase I/II trial was recently uploaded to an open-access repository [[203](#ref-UJnnQNkx)]. This part of the trial was designed to identify which dosing regimen should move forward into late phase clinical trials. Both younger (18-59 years) and older patients (60-84 years) were randomly assigned to receive either 5 μg or 25 μg Novavax-CoV2373 or placebo in two doses, 21 days apart. In line with the phase I data, reactogenicity remained mild to moderate and of short duration. Both dose levels were able to induce high anti-spike IgG titers as well as neutralizing antibody responses after the second dose. Based on both safety and efficacy data, the 5 μg dosing regimen was selected as the optimal dose regiment for the ongoing phase III trial. Although the phase III trial data has not been published yet, Novavax announced an efficacy of 89.3% based on their phase 3 trial in the UK and South Africa. This trial included over 15,000 participants in the UK and 4,000 participants in South Africa with occurrence of a PCR-confirmed symptomatic case as the primary endpoint. In the first interim analysis (U.K.), 56 cases of COVID-19 were observed in the placebo group compared to 6 cases in the treatment group. Importantly, the vaccine candidate also shows significant clinical efficacy against the prevalent UK and South African variants. The company has also initiated the development of new constructs to select candidates that can be used as a booster against new strains and plans to initiate clinical trials for these new constructs in the second quarter of 2021.

## 1.5 Vaccine Development Summary

## 1.6 Complementary Approaches to Vaccine Development

### 1.6.1 Adjuvants for Vaccines

Adjuvants include a variety of molecules or larger microbial-related products that have an effect on the immune system or an immune response of interest. They can either be comprised of or contain immunostimulants or immunomodulators. Adjuvants are sometimes included within vaccines, especially vaccines other than live-attenuated and inactivated viruses, in order to enhance the immune response. A review on the development of SARS-CoV-2 vaccines [[204](#ref-ouOXy0wH)] also included a brief summary of the potential of adjuvants for these vaccines, including a brief description of some already commonly used adjuvants. Different adjuvants can regulate different types of immune responses, so the type or combination of adjuvants used in a vaccine will depend on both the type of vaccine and concern related to efficacy and safety. A variety of possible mechanisms for adjuvants have been researched [[205](#ref-13bVbfc5h),[206](#ref-122h6fIxE),[207](#ref-uO0uqhxc)], including the following: induction of DAMPs that can be recognized by certain PRRs of the innate immune system; functioning as PAMP that can also be recognized by certain PRRs; and more generally enhancing the humoral or cellular immune responses. Selection of one or more adjuvants requires considering how to promote the advantageous effects of the components and/or immune response and, likewise, to inhibit possible deleterious effects. There are also considerations related to the method of delivering (or co-delivering) the adjuvant and antigen components of a vaccine.

### 1.6.2 Trained Immunity

Another approach that is being investigated explores the potential for vaccines that are not made from the SARS-CoV-2 virus to confer what has been termed trained immunity. In a recent review [[208](#ref-103fS7Kz2)], trained immunity was defined as forms of memory that are temporary (e.g., months or years) and reversible. It is induced by exposure to whole-microorganism vaccines or other microbial stimuli that generates heterologous protective effects. Trained immunity can be displayed by innate immune cells or innate immune features of other cells, and it is characterized by alterations to immune responsiveness to future immune challenges due to epigenetic and metabolic mechanisms. These alterations can take the form of either an increased or decreased response to immune challenge by a pathogen. Trained immunity elicited by non-SARS-CoV-2 whole-microorganism vaccines could potentially improve SARS-CoV-2 susceptibility or severity [[209](#ref-Vu1VILWK)].

One type of stimulus which research indicates can induce trained immunity is bacillus Calmette-Guerin (BCG) vaccination. BCG is an attenuated form of bacteria *Mycobacterium bovis*. The vaccine is most commonly administered for the prevention of tuberculosis in humans. Clinical trials in non-SARS-CoV-2-infected adults have been designed to assess whether BCG vaccination could have prophylactic effects against SARS-CoV-2 by reducing susceptibility, preventing infection, or reducing disease severity. A number of trials are now evaluating the effects of the BCG vaccine or the related vaccine VPM1002 [[31](#ref-9m3rP633),[32](#ref-xdqxBruc),[209](#ref-Vu1VILWK),[210](#ref-y9IYdfM3),[211](#ref-962rELVS),[212](#ref-EuwTWcPi),[213](#ref-dQtUeruv),[214](#ref-DjXsPR8O),[215](#ref-10OE6y3Pv),[216](#ref-86OjIybR),[217](#ref-ITO15LIz),[218](#ref-VkZGZxLn),[219](#ref-13JVjMfQI),[220](#ref-nk2MVsld),[221](#ref-1E2t9tr8h)].

The ongoing trials are using a number of different approaches. Some trials enroll healthcare workers, other trials hospitalized elderly adults without immunosuppression who get vaccinated with placebo or BCG at hospital discharge, and yet another set of trials older adults (>50 years) under chronic care for conditions like hypertension and diabetes. One set of trials, for example, uses time until first infection as the primary study endpoint; more generally, outcomes measured in some of these trials are related to incidence of disease and disease severity or symptoms. Some analyses have suggested a possible correlation at the country level between the frequency of BCG vaccination (or BCG vaccination policies) and the severity of COVID-19 [[209](#ref-Vu1VILWK)]. Currently it is unclear whether this correlation has any connection to trained immunity. Many possible confounding factors are also likely to vary among countries, such as age distribution, detection efficiency, stochastic epidemic dynamic effects, differences in healthcare capacity over time in relation to epidemic dynamics, and these have not been adequately accounted for in current analyses. It is unclear whether there is an effect of the timing of BCG vaccination, both during an individual’s life cycle and relative to the COVID-19 pandemic. Additionally, given that severe SARS-CoV-2 may be associated with a dysregulated immune response, it is unclear what alterations to the immune response would be most likely to be protective versus pathogenic (e.g., [[209](#ref-Vu1VILWK),[222](#ref-i5k18bpX),[223](#ref-1GnFL9zeN),[224](#ref-1228YjPRv)]). The article [[209](#ref-Vu1VILWK)] proposes that trained immunity might lead to an earlier and stronger response, which could in turn reduce viremia and the risk of later, detrimental immunopathology. While trained immunity is an interesting possible avenue to complement vaccine development efforts through the use of an existing vaccine, additional research is required to assess whether the BCG vaccine is likely to confer trained immunity in the case of SARS-CoV-2.

## 1.7 Viral evolution and vaccine protection

With these vaccines in place, one concern is how the virus’s continued evolution will affect their efficacy. Since the start of this pandemic, we have already seen multiple variants emerge: B.1.1.7, which emerged in the UK, B.1.351, which emerged in South Africa, and P.1, which emerged in Brazil.

Viruses evolve or mutate at different rates. Mutation rate is measured as the number of substitutions per nucleotide per cell infected (μs/n/c) [[225](#ref-4sZmtyNk)]. RNA viruses tend to have mutation rates between 10-6 to 10-4 [[225](#ref-4sZmtyNk)]. As a reference, influenza A virus has a mutation rate of 10-5, whereas the mutation rate of SARS-CoV-2 is lower, with the mutation rate estimated at 10-6 [[226](#ref-vESqa6V0)]. The accumulation of mutations allows the virus to escape recognition by the immune system [[227](#ref-2pzbGZvL)].

The efficacy of vaccines depends on their ability to train the immune system to recognize the virus. Therefore, viruses can develop resistance to vaccines through the accumulation of mutations that affect recognition. The lower mutation rate of SARS-CoV-2 suggests the possibility of SARS-CoV-2 vaccines having a more long-lasting effect compared to vaccines targeting the influenza A virus.

The current SARS-CoV-2 vaccines in distribution have been reported to provide similar efficacy against the B.1.1.7 variant compared to the variants common at the time they were developed but reduced efficacy against the B.1.351 variant [[228](#ref-LxJvckNs)]. Pfizer and Moderna announced that they are working on developing a booster shot to improve efficacy against the B.1.351 variant [[229](#ref-ZxfNX9xk)/]. The WHO continues to monitor the emergence of variants and their impact on vaccine efficacy [[230](#ref-lY0XUlUp)]. Previous research in the computational prediction of the efficacy of vaccines targeting the influenza A virus might complement efforts to monitor these types of viral outbreaks [[231](#ref-YlAWEwlx)]. To adapt, future vaccines may need to account for multiple variants and strains of SARS-CoV-2, and booster shots may be required [[232](#ref-180UFKjJ2)].

## 1.8 Global Vaccine Status and Distribution

The unprecedented development of COVID-19 vaccines in under a year since the beginning of the pandemic now requires 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 [[233](#ref-RG0vzlcE),[234](#ref-19CWe6pdS),[235](#ref-d0kUYq5Z)]. 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 [[236](#ref-S8WhufUV),[237](#ref-dLbKv1xi),[238](#ref-jbpdQdOw),[239](#ref-z5c17nGB),[240](#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 [[241](#ref-sEyIoYCS)]. As of March 6th, 2021, approximately 319 million vaccine doses have been administered in at least 118 countries worldwide using 10 different vaccines [[60](#ref-DQmAgN0V)/,[242](#ref-dfl5iCJI)]. The global vaccination rate is currently ~8.1 million doses per day, which at the current rate would take almost 4 years to vaccinate 75% of the world’s population according to media estimates of a two-dose regimen [[60](#ref-DQmAgN0V)/]. 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 [[243](#ref-kL8PlRJu)].

In North America, the majority of vaccines distributed until March 2021 have been produced by Pfizer-BioNTech and Moderna. In Canada, the vaccine approval process is conducted by Health Canada, which uses a fast-tracked process whereby vaccine producers can submit data as it becomes available to allow for rapid review. An approval may be granted following reviews of the available phase III clinical data. This is followed by a period of pharmacovigilance in the population using their post-market surveillance system, which will monitor the long-term safety and efficacy of any vaccines [[244](#ref-41tJkg7h),[245](#ref-YPaDf9jp)]. Health Canada has authorized the use of the Pfizer (December 9th, 2020), Moderna (December 23rd, 2020), Oxford-AstraZeneca (February 26th, 2021), and the Janssen (March 5th, 2021) vaccines, and the Novavax Inc vaccine is also under consideration [[246](#ref-15t1ePH1z)]. While Canada initially projected that by the end of September 2021 a vaccine would be available for all Canadian adults, they now predict that it may be possible earlier as more vaccines have been approved and become available [[247](#ref-fQM1moSe)].

In the U.S., vaccines are required to have demonstrated safety and efficacy in phase III trials before manufacturers apply for an emergency use authorization (EUA) from the FDA. If an EUA is granted, an additional evaluation of the safety and efficacy of the vaccines is conducted by the CDC’s Advisory Committee on Immunization Practices (ACIP) who also provide guidance on vaccine prioritization. On December 1st, 2020, ACIP provided an interim phase 1a recommendation that healthcare workers and long-term care facility residents should be the first to be offered any vaccine approved [[248](#ref-18BMz232x)]. This was shortly followed by an EUA on December 11th, 2020 for the use of the Pfizer-BioNTech COVID vaccine [[249](#ref-17wU8KTSP)], which was distributed and administered to the first healthcare workers on December 14th, 2020 [[250](#ref-123cVqUNO)]. Shortly thereafter, an EUA for the Moderna vaccine was issue on December 18th, 2020 [[251](#ref-7yAHeCqZ)]. On December 20th, 2020, ACIP updated their initial recommendations to suggest that vaccinations should be offered to people aged 75 years old and older and to non-healthcare frontline workers in phase 1b [[252](#ref-Y3jvGtR9)]. On the same date, it was recommended that phase 1c should include people aged 65-74 years old, individuals between the ages of 16-74 years old at high-risk due to health conditions, and essential workers ineligible in phase 1b [[252](#ref-Y3jvGtR9)]. On the following day, December 21st, 2020, the first Moderna vaccines used outside of clinical trials were administered to American healthcare workers, which was the same day that President-elect Biden and Dr. Biden received their first doses of the Pfizer-BioNTech vaccine live on television to instill confidence in the approval and vaccination process [[253](#ref-f5yIh2Xp)].

On February 27th, 2020, the FDA issued an EUA for the Janssen COVID-19 Vaccine [[254](#ref-BG7N9ETs)]. This was followed by an update on recommendations by ACIP for the use of the Janssen COVID-19 vaccine for those over 18 years old [[255](#ref-yNaiGtW1)]. The Janssen vaccine was first distributed to healthcare facilities on March 1st, 2021. On March 12, 2021, the WHO added the Janssen vaccine to the list of safe and effective emergency tools for COVID-19 [[256](#ref-Vd1wOy6d)]. While the CDC’s ACIP can provide recommendations, it is up to the public health authorities of each state, territory, and tribe to interpret the guidance and determine who will be vaccinated first [[257](#ref-1CcsUnCiw)]. Prior to distribution of the Janssen vaccine, over 103 million doses of the Moderna and Pfizer-BioNTech vaccines were delivered across the U.S., with almost 79 million doses administered. Of the total population, 15.6% have received at least one dose and 7.9% have received a second dose of either the Moderna (~38.3 million) or the Pfizer-BioNTech (~40.2 million) vaccines by February 28th, 2021 [[258](#ref-1Bv67ENp2)/#vaccinations]. President Biden’s administration has predicted that by the end of May 2021 there may be enough vaccine supply available for all adults in the U.S. [[259](#ref-ZkZ6ToLh),[260](#ref-13bndHWdk)]. However, vaccine production, approval, and distribution was not straightforward in the U.S., as information was initially sparse and the rollout of vaccines was complicated by poor planning and leadership due to political activities prior to the change of administration in January 2021 [[261](#ref-XOLE6iJT)]. These political complications highlight the importance of the transparent vaccine approval process conducted by the FDA [[262](#ref-1Bgnim0gX)].

Outside the U.S., the Moderna and Pfizer-BioNTech vaccines have been administered in 29 and 69 other countries, respectively, mainly in Europe and North America [[242](#ref-dfl5iCJI)]. The Janssen vaccine has so far only been administered in South Africa and the U.S. [[242](#ref-dfl5iCJI),[263](#ref-I0vakLIc)], but it has also been approved in Bahrain, the European Union (E.U.), Iceland, Liechtenstein, and Norway [[59](#ref-wByD9WaX)]. On March 11th, 2021, Johnson & Johnson received approval from the European Medicines Agency (EMA) for conditional marketing authorization of their vaccine [[264](#ref-17BEDzTkD)]. Notably, on March 2nd, 2021, rivals Johnson & Johnson and Merck announced that they entered an agreement to increase production of the Janssen vaccine to meet global demand [[265](#ref-hHW8U8rE)/].

The U.K. was the first country to approve use of the Pfizer-BioNTech vaccine on December 2nd, 2020 [[266](#ref-133HGZMEL)], and it was later approved by EMA on December 21st, 2020 [[267](#ref-G6V3FR6V)]. The U.K. was also the first to administer the Pfizer-BioNTech vaccine, making it the first COVID-19 vaccine supported by phase III data to be administered outside of clinical trials on December 8th, 2020. The Oxford-AstraZeneca vaccine, was approved by the Medicines and Healthcare Products Regulatory Agency (MHRA) in the U.K. and by EMA in the E.U. on December 30th (2020) [[268](#ref-1HIxYDTsj)] and January 29th (2021) [[269](#ref-bbw8sMvc)] respectively. The Oxford-AstraZeneca vaccine was first administered in the UK on January 4th, 2021 [[270](#ref-q1Ui5Fm8)], and it is now being used in 53 countries in total, including Brazil, India, Pakistan, Mexico, and spanning most of Europe [[242](#ref-dfl5iCJI)]. The Moderna vaccine was authorized for use in the E.U. by EMA on January 6th, 2021 [[271](#ref-JPSLcRBY)] and in the U.K. by MHRA on January 8th, 2021 [[272](#ref-k9X9pXJe)]. As of March 5th, 2021, 22 million people in the U.K. had received at least one vaccine dose [[273](#ref-cWMPXfju)].

While the Pfizer-BioNTech vaccine was the first to be distributed following phase III clinical trials, the first COVID-19 vaccine to be widely administered to people prior to the completion of phase III clinical trials was Sputnik V. Sputnik V was administered to as many as 1.5 million Russians by early January [[110](#ref-X5LkVfY6)/] due to the establishment of mass vaccination clinics in December 2020, prior to which only approximately 100,000 Russians had already been vaccinated [[274](#ref-uvQMgFXB),[275](#ref-Vwv7l7Hd)/?sh=50650e4e62e1]. Doses of Sputnik V have also been distributed to other parts of Europe, such as Belarus, Bosnia-Herzegovina, Hungary, San Marino, Serbia, and Slovakia [[111](#ref-16LczMwFO),[112](#ref-Z0V7NK7Y),[113](#ref-16GYKbrOq)], with the Czech Republic and Austria also having expressed interest in its procurement [[114](#ref-125VEHWS7)]. Hungary was the first E.U. member country to approve and distribute Sputnik V outside of Russia [[114](#ref-125VEHWS7)], despite the EMA stating that they had neither approved nor received a request for approval of Sputnik V [[276](#ref-P6x0Qy6s)]. Hungary is also in talks with China to procure the Sinopharm vaccines, which have been approved by Hungarian health authorities but also have not received approval by EMA in the E.U. [[114](#ref-125VEHWS7)]. In Latin America, production facilities in both Brazil and Argentina will allow for increased production capacity of Sputnik V and doses have been distributed to Mexico, Argentina, Bolivia, Nicaragua, Paraguay, and Venezuela [[277](#ref-ID8IywJM)/]. Guinea was the first African nation to administer Sputnik V in December 2020, and the Central African Republic, Zimbabwe, and the Ivory Coast have all registered their interest in purchasing doses of the vaccine [[277](#ref-ID8IywJM)/]. In the Middle East, Iran has received its first doses of Sputnik V and the United Arab Emirates is conducting phase III trials [[277](#ref-ID8IywJM)/]. In Asia, while China’s vaccine candidates are favored, the Philippines, Nepal, and Uzbekistan have sought Sputnik V doses [[278](#ref-160U0Yb7M)/,[278](#ref-160U0Yb7M)/]. In total, the RDIF claims to have received orders totalling 1.2 billion doses by over 50 countries worldwide [[278](#ref-160U0Yb7M)/] and at least 18 countries are currently administering Sputnik V around the globe [[242](#ref-dfl5iCJI)]. Sputnik V has been an attractive vaccine for many countries due to its relatively low price, high efficacy, and its favorable storage conditions. For some countries, Russia and China have also been more palatable politically than vaccine suppliers in the West [[277](#ref-ID8IywJM)/,[279](#ref-FAQXPsyc)]. For others, the delays in the distribution of the other, more-favored candidates has been a motivating factor for pursuing the Sputnik V and Chinese alternatives [[112](#ref-Z0V7NK7Y),[279](#ref-FAQXPsyc)]. Additionally, Germany has stated that if Sputnik V were approved by EMA, it would be considered by the E.U. [[280](#ref-zCPl6A82)]. Russia is developing other vaccine candidates and has approved a third vaccine, CoviVac, which is an inactivated vaccine produced by the Chumakov Centre in Moscow, despite the fact the clinical trials have yet to begin [[281](#ref-hpScvlYg)].

In Asia, China and India are the main COVID-19 vaccination developers and providers. In India, the Covaxin vaccine produced by Bharat Biotech received emergency authorization on January 3rd, 2021, despite the lack of phase III data until March 3rd [[48](#ref-Ks3L7qHG)]. Following the release of the phase III data indicating 81% efficacy, Zimbabwe authorized the use of Covaxin [[53](#ref-13yEnvOyP)]. 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 [[54](#ref-P9mD7Gc9)]. Notably, Novavax has signed an agreement with the Serum Institute of India allowing them to produce up to 2 billion doses a year [[57](#ref-e8pnj0O3)]. Novavax has also signed agreements with the U.K., Canada, Australia, and South Korea [[58](#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 [[59](#ref-wByD9WaX)]. India has vaccinated approximately 24 million people [[60](#ref-DQmAgN0V)/]. This has been achieved by mainly using the AstraZeneca-University of Oxford vaccine, known as Covishield in India, which is also produced by the Serum Institute of India, and using India’s own Covaxin vaccine [[61](#ref-gsNWcXHn)]. India has also shipped approximately 58 million COVID-19 vaccines to 66 countries [[62](#ref-QRYET3sK)] Considering India produces approximately 60% of the world’s vaccines prior to the pandemic, it is no surprise that several other vaccine candidates are under development. These include ZyCov-Di, a DNA vaccine produced by Zydus Cadila, HGCO19, India’s first mRNA vaccine produced by Genova and HDT Biotech Corporation (of the U.S.), and the Bio E subunit vaccine produced by Biological E in collaboration with U.S.-based Dynavax and the Baylor College of Medicine [[61](#ref-gsNWcXHn)].

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. This vaccine is currently approved for use in Bahrain, China, and the United Arab Emirates, but has been granted emergency use in Argentina, Cambodia, Egypt, Guyana, Hungary, Iran, Iraq, Jordan, Nepal, Pakistan, Peru, Venezuela, and Zimbabwe, with limited use in both Serbia and the Seychelles [[64](#ref-rqDwcy2A)]. The Sinovac vaccine, CoronaVac, has been approved for use in China, and has been granted emergency use in Azerbaijan, Brazil, Cambodia, Chile, Colombia, Ecuador, Hong Kong, Indonesia, Laos, Malaysia, Mexico, Philippines, Thailand, Turkey, Ukraine, and Uruguay [[63](#ref-ONBMyjqX)]. Sinovac has reported that their platform now has the capacity to provide up to a billion doses [[63](#ref-ONBMyjqX)]. 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 [[66](#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 [[65](#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 III trials [[282](#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 [[262](#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 [[66](#ref-gdTtuj5e)]. 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 [[66](#ref-gdTtuj5e)]. Similar delays and shortages of doses promised have been reported by officials in the Philippines, Egypt, Morocco, and the United Arab Emirates [[67](#ref-XJmfG8HD),[68](#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 [[68](#ref-12zVLzkpB)].

Globally, North America currently leads the world vaccination rates (13.8 per 100 people) followed by Europe (8.2 per 100), South America (3.1 per 100), Asia (1.9 per 100), Africa (0.3 per 100), and Oceania (0.1 per 100) are trailing behind [[242](#ref-dfl5iCJI)]. Considering the wealthy nations of North America and Europe have secured most of the limited COVID-19 vaccine stocks [[283](#ref-1AvwH3T5y)], it is likely that low- and middle-income countries will face further competition with Western countries for vaccine availability. 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 [[284](#ref-1EnpYQzIq)]. COVAX is 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 [[285](#ref-3Gq7ETv7),[286](#ref-KzHIbPMY)]. COVAX invested in several vaccine programs to ensure they would have access to successful vaccine candidates [[287](#ref-1H0PiQpLz)]. The COVAX plan ensured 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 [[288](#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 [[243](#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 [[289](#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 [[290](#ref-sr5oRBgc)]. 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 [[284](#ref-1EnpYQzIq),[291](#ref-2b6FdDOy)]. However, much further progress is required when only 0.3 per 100 people have been vaccinated in Africa [[242](#ref-dfl5iCJI)].

## 1.9 Discussion

Additionally, major advances in vaccines using mRNA and adenoviruses that have led to three vaccines becoming available or close to becoming available in late 2020 (Figure ??).

Though some concerns remain about the duration of sustained immunity for convalescents, vaccine development efforts are ongoing and show initial promising results. The Moderna trial, for example, reported that the neutralizing activity in participants who received two doses of the vaccine was similar to that observed in convalescent plasma.

One of the two mRNA vaccines, Pfizer and BioNTech’s BNT162b2, has been issued an EUA for patients as young as 16 [[292](#ref-1DETimS2y)], while ModernaTX has begun a clinical trial to assess its mRNA vaccine in adolescents ages 12 to 18 [[293](#ref-eDdKGPvy)].

# 2 Additional Items

## 2.1 Competing Interests

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

## 2.2 Author Contributions

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

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# 3 References

1. **History of vaccination** S 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. **Neutralizing Monoclonal Antibodies as Promising Therapeutics against Middle East Respiratory Syndrome Coronavirus Infection** Hui-Ju Han, Jian-Wei Liu, Hao Yu, Xue-Jie Yu *Viruses* (2018-11-30) <https://doi.org/ggp87v> DOI: [10.3390/v10120680](https://doi.org/10.3390/v10120680) · PMID: [30513619](https://www.ncbi.nlm.nih.gov/pubmed/30513619) · PMCID: [PMC6315345](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6315345)

3. **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)

4. **“Variolation” and Vaccination in Late Imperial China, Ca 1570–1911** Angela Ki Che Leung *Springer Science and Business Media LLC* (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)

5. **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)

6. **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)

7. **Vaccines, new opportunities for a new society** R Rappuoli, M Pizza, G Del Giudice, E 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)

8. **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)

9. **The Cutter Incident, 50 Years Later** Paul A Offit *New England Journal of Medicine* (2005-04-07) <https://doi.org/cw7wzx> DOI: [10.1056/nejmp048180](https://doi.org/10.1056/nejmp048180) · PMID: [15814877](https://www.ncbi.nlm.nih.gov/pubmed/15814877)

10. **DNA** <https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/vaccines-quality/dna>

11. **DNA vaccines: ready for prime time?** Michele A Kutzler, David B Weiner *Nature Reviews Genetics* (2008-10) <https://doi.org/fvzwbs> DOI: [10.1038/nrg2432](https://doi.org/10.1038/nrg2432) · PMID: [18781156](https://www.ncbi.nlm.nih.gov/pubmed/18781156) · PMCID: [PMC4317294](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4317294)

12. **mRNA vaccines — a new era in vaccinology** Norbert Pardi, Michael J Hogan, Frederick W Porter, Drew Weissman *Nature Reviews Drug Discovery* (2018-01-12) <https://doi.org/gcsmgr> DOI: [10.1038/nrd.2017.243](https://doi.org/10.1038/nrd.2017.243) · PMID: [29326426](https://www.ncbi.nlm.nih.gov/pubmed/29326426) · PMCID: [PMC5906799](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5906799)

13. **Recent innovations in mRNA vaccines** Jeffrey B Ulmer, Andrew J Geall *Current Opinion in Immunology* (2016-08) <https://doi.org/f82bgg> DOI: [10.1016/j.coi.2016.05.008](https://doi.org/10.1016/j.coi.2016.05.008) · PMID: [27240054](https://www.ncbi.nlm.nih.gov/pubmed/27240054)

14. **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)

15. **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)

16. **Newer Vaccine Technologies Deployed to Develop COVID-19 Shot** Abby Olena *The Scientist Magazine* (2020-02-21) <https://www.the-scientist.com/news-opinion/newer-vaccine-technologies-deployed-to-develop-covid-19-shot-67152>

17. **Pathogenesis, Symptomatology, and Transmission of SARS-CoV-2 through analysis of Viral Genomics and Structure** Halie M Rando, Adam L MacLean, Alexandra J Lee, Sandipan Ray, Vikas Bansal, Ashwin N Skelly, Elizabeth Sell, John J Dziak, Lamonica Shinholster, Lucy D'Agostino McGowan, … Casey S Greene *arXiv* (2021-02-15) <https://arxiv.org/abs/2102.01521>

18. **WHO | Novel Coronavirus – China** WHO <http://www.who.int/csr/don/12-january-2020-novel-coronavirus-china/en/>

19. **Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK** Merryn Voysey, Sue Ann Costa Clemens, Shabir A Madhi, Lily Y Weckx, Pedro M Folegatti, Parvinder K Aley, Brian Angus, Vicky L Baillie, Shaun L Barnabas, Qasim E Bhorat, … Peter Zuidewind *The Lancet* (2021-01) <https://doi.org/fmq2> DOI: [10.1016/s0140-6736(20)32661-1](https://doi.org/10.1016/s0140-6736(20)32661-1) · PMID: [33306989](https://www.ncbi.nlm.nih.gov/pubmed/33306989) · PMCID: [PMC7723445](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7723445)

20. **The SARS-CoV-2 Spike Glycoprotein Biosynthesis, Structure, Function, and Antigenicity: Implications for the Design of Spike-Based Vaccine Immunogens** Liangwei Duan, Qianqian Zheng, Hongxia Zhang, Yuna Niu, Yunwei Lou, Hui Wang *Frontiers in Immunology* (2020-10-07) <https://doi.org/gjkthw> DOI: [10.3389/fimmu.2020.576622](https://doi.org/10.3389/fimmu.2020.576622) · PMID: [33117378](https://www.ncbi.nlm.nih.gov/pubmed/33117378) · PMCID: [PMC7575906](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7575906)

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

22. **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>

23. **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)

24. **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)

25. **Vaccine Immunology** Claire-Anne Siegrist *Elsevier BV* (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)

26. **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>

27. **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)

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

29. **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)

30. **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)

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. **Non-specific effects of BCG vaccine on viral infections** SJCFM Moorlag, RJW Arts, R van Crevel, MG Netea *Clinical Microbiology and Infection* (2019-12) <https://doi.org/ggq62z> DOI: [10.1016/j.cmi.2019.04.020](https://doi.org/10.1016/j.cmi.2019.04.020) · PMID: [31055165](https://www.ncbi.nlm.nih.gov/pubmed/31055165)

34. **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)

35. **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/>

36. **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/>

37. **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* (2021-07-20) <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)

38. **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>

39. **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>

40. **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)

41. **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)

42. **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)

43. **A Review of the Progress and Challenges of Developing a Vaccine for COVID-19** Omna Sharma, Ali A Sultan, Hong Ding, Chris R Triggle *Frontiers in Immunology* (2020-10-14) <https://doi.org/gh65wd> DOI: [10.3389/fimmu.2020.585354](https://doi.org/10.3389/fimmu.2020.585354) · PMID: [33163000](https://www.ncbi.nlm.nih.gov/pubmed/33163000) · PMCID: [PMC7591699](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7591699)

44. **Double-Blind, Randomized, Placebo-Controlled Phase III Clinical Trial to Evaluate the Efficacy and Safety of treating Healthcare Professionals with the Adsorbed COVID-19 (Inactivated) Vaccine Manufactured by Sinovac – PROFISCOV: A structured summary of a study protocol for a randomised controlled trial** Ricardo Palacios, Elizabeth González Patiño, Roberta de Oliveira Piorelli, Monica Tilli Reis Pessoa Conde, Ana Paula Batista, Gang Zeng, Qianqian Xin, Esper G Kallas, Jorge Flores, Christian F Ockenhouse, Christopher Gast *Trials* (2020-10-15) <https://doi.org/ghjkrh> DOI: [10.1186/s13063-020-04775-4](https://doi.org/10.1186/s13063-020-04775-4) · PMID: [33059771](https://www.ncbi.nlm.nih.gov/pubmed/33059771) · PMCID: [PMC7558252](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7558252)

45. **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)

46. **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)

47. **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)

48. **Bharat Biotech Announces Phase 3 Results of COVAXIN** Bharat Biotech (2021-03-03) <https://www.bharatbiotech.com/images/press/covaxin-phase3-efficacy-results.pdf>

49. **Ocugen's COVID-19 Vaccine Co-Development Partner, Bharat Biotech shares Phase 3 Interim Results of COVAXIN, Demonstrates Efficacy of 81%** Biogenetech (2021-03-05) <https://www.biogenetech.co.th/wp-content/uploads/2021/03/5-Ocugen.pdf>

50. **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)

51. **Neutralization of UK-variant VUI-202012/01 with COVAXIN vaccinated human serum** Gajanan N Sapkal, Pragya D Yadav, Raches Ella, Gururaj R Deshpande, Rima R Sahay, Nivedita Gupta, VKrishna Mohan, Priya Abraham, Samiran Panda, Balram Bhargava *Cold Spring Harbor Laboratory* (2021-01-27) <https://doi.org/gjmttm> DOI: [10.1101/2021.01.26.426986](https://doi.org/10.1101/2021.01.26.426986)

52. **#IndiaFightsCorona COVID-19** MyGov.in (2020-03-16) <https://mygov.in/covid-19/>

53. **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>

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

55. **Immunogenic Potential of DNA Vaccine candidate, ZyCoV-D against SARS-CoV-2 in Animal Models** Ayan Dey, TM Chozhavel Rajanathan, Harish Chandra, Hari PR Pericherla, Sanjeev Kumar, Huzaifa S Choonia, Mayank Bajpai, Arun K Singh, Anuradha Sinha, Gurwinder Saini, … Kapil Maithal *Cold Spring Harbor Laboratory* (2021-01-26) <https://doi.org/gjmttn> DOI: [10.1101/2021.01.26.428240](https://doi.org/10.1101/2021.01.26.428240)

56. **Vaccine information, ICMR New delhi - COVID-19 Vaccine** <https://vaccine.icmr.org.in/covid-19-vaccine>

57. **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>

58. **Novavax Investor Relations - Press Releases & Statements** <https://ir.novavax.com/press-releases>

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

60. **Bloomberg - Are you a robot?** <https://www.bloomberg.com/tosv2.html?vid=&uuid=9c992f66-1a1d-11ec-a705-444f784a4170&url=L2dyYXBoaWNzL2NvdmlkLXZhY2NpbmUtdHJhY2tlci1nbG9iYWwtZGlzdHJpYnV0aW9u>

61. **Zydus Cadila: What we know about India's new Covid vaccines** BBC News (2021-08-23) <https://www.bbc.com/news/world-asia-india-55748124>

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

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

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

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

66. **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>

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

68. **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>

69. **Vaccine Design** Pharmaceutical Biotechnology *Springer Science and Business Media LLC* (1995) <https://doi.org/gh3zp9> DOI: [10.1007/978-1-4615-1823-5](https://doi.org/10.1007/978-1-4615-1823-5)

70. **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)

71. **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)

72. **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)

73. **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)

74. **Novavax Investor Relations - Press Releases & Statements** <https://ir.novavax.com/press-releases>

75. **Safety, Tolerability and Immunogenicity of INO-4800 for COVID-19 in Healthy Volunteers - Full Text View - ClinicalTrials.gov** <https://clinicaltrials.gov/ct2/show/NCT04336410>

76. **Electroporation delivery of DNA vaccines: prospects for success** Niranjan Y Sardesai, David B Weiner *Current Opinion in Immunology* (2011-06) <https://doi.org/cq8b4p> DOI: [10.1016/j.coi.2011.03.008](https://doi.org/10.1016/j.coi.2011.03.008) · PMID: [21530212](https://www.ncbi.nlm.nih.gov/pubmed/21530212) · PMCID: [PMC3109217](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3109217)

77. **Tolerability of intramuscular and intradermal delivery by CELLECTRA <sup>®</sup> adaptive constant current electroporation device in healthy volunteers** Malissa C Diehl, Jessica C Lee, Stephen E Daniels, Pablo Tebas, Amir S Khan, Mary Giffear, Niranjan Y Sardesai, Mark L Bagarazzi *Human Vaccines & Immunotherapeutics* (2014-10-27) <https://doi.org/ggrj7h> DOI: [10.4161/hv.24702](https://doi.org/10.4161/hv.24702) · PMID: [24051434](https://www.ncbi.nlm.nih.gov/pubmed/24051434) · PMCID: [PMC3906411](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3906411)

78. **Multivalent and Multipathogen Viral Vector Vaccines** Katharina B Lauer, Ray Borrow, Thomas J Blanchard *Clinical and Vaccine Immunology* (2017-01) <https://doi.org/f9tsw2> DOI: [10.1128/cvi.00298-16](https://doi.org/10.1128/cvi.00298-16) · PMID: [27535837](https://www.ncbi.nlm.nih.gov/pubmed/27535837) · PMCID: [PMC5216423](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5216423)

79. **Viral vectors as vaccine platforms: from immunogenicity to impact** Katie J Ewer, Teresa Lambe, Christine S Rollier, Alexandra J Spencer, Adrian VS Hill, Lucy Dorrell *Current Opinion in Immunology* (2016-08) <https://doi.org/f82tb6> DOI: [10.1016/j.coi.2016.05.014](https://doi.org/10.1016/j.coi.2016.05.014) · PMID: [27286566](https://www.ncbi.nlm.nih.gov/pubmed/27286566)

80. **Clinical Assessment of a Novel Recombinant Simian Adenovirus ChAdOx1 as a Vectored Vaccine Expressing Conserved Influenza A Antigens** Richard D Antrobus, Lynda Coughlan, Tamara K Berthoud, Matthew D Dicks, Adrian VS Hill, Teresa Lambe, Sarah C Gilbert *Molecular Therapy* (2014-03) <https://doi.org/f5vhv3> DOI: [10.1038/mt.2013.284](https://doi.org/10.1038/mt.2013.284) · PMID: [24374965](https://www.ncbi.nlm.nih.gov/pubmed/24374965) · PMCID: [PMC3944330](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3944330)

81. **Vaccine Candidates against Coronavirus Infections. Where Does COVID-19 Stand?** Jawad Al-Kassmy, Jannie Pedersen, Gary Kobinger *Viruses* (2020-08-07) <https://doi.org/ghsfmc> DOI: [10.3390/v12080861](https://doi.org/10.3390/v12080861) · PMID: [32784685](https://www.ncbi.nlm.nih.gov/pubmed/32784685) · PMCID: [PMC7472384](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7472384)

82. **Poxviruses as vaccine vectors** P-P Pastoret, A Vanderplasschen *Comparative Immunology, Microbiology and Infectious Diseases* (2003-10) <https://doi.org/cnw6vw> DOI: [10.1016/s0147-9571(03)00019-5](https://doi.org/10.1016/s0147-9571(03)00019-5)

83. **Enhancing poxvirus vectors vaccine immunogenicity** Juan García-Arriaza, Mariano Esteban *Human Vaccines & Immunotherapeutics* (2014-05-05) <https://doi.org/ghz9tw> DOI: [10.4161/hv.28974](https://doi.org/10.4161/hv.28974) · PMID: [25424927](https://www.ncbi.nlm.nih.gov/pubmed/25424927) · PMCID: [PMC4896794](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4896794)

84. **New Insights on Adenovirus as Vaccine Vectors** Marcio O Lasaro, Hildegund CJ Ertl *Molecular Therapy* (2009-08) <https://doi.org/dcz549> DOI: [10.1038/mt.2009.130](https://doi.org/10.1038/mt.2009.130) · PMID: [19513019](https://www.ncbi.nlm.nih.gov/pubmed/19513019) · PMCID: [PMC2835230](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2835230)

85. **Attenuated vesicular stomatitis viruses as vaccine vectors.** A Roberts, L Buonocore, R Price, J Forman, JK Rose *Journal of virology* (1999-05) <https://www.ncbi.nlm.nih.gov/pubmed/10196265> DOI: [10.1128/jvi.73.5.3723-3732.1999](https://doi.org/10.1128/jvi.73.5.3723-3732.1999) · PMID: [10196265](https://www.ncbi.nlm.nih.gov/pubmed/10196265) · PMCID: [PMC104148](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC104148)

86. **Vesicular stomatitis virus: re-inventing the bullet** Brian D Lichty, Anthony T Power, David F Stojdl, John C Bell *Trends in Molecular Medicine* (2004-05) <https://doi.org/fg6wv5> DOI: [10.1016/j.molmed.2004.03.003](https://doi.org/10.1016/j.molmed.2004.03.003) · PMID: [15121047](https://www.ncbi.nlm.nih.gov/pubmed/15121047)

87. **Viral vectors as vaccine platforms: deployment in sight** Christine S Rollier, Arturo Reyes-Sandoval, Matthew G Cottingham, Katie Ewer, Adrian VS Hill *Current Opinion in Immunology* (2011-06) <https://doi.org/d8p72q> DOI: [10.1016/j.coi.2011.03.006](https://doi.org/10.1016/j.coi.2011.03.006) · PMID: [21514130](https://www.ncbi.nlm.nih.gov/pubmed/21514130)

88. **Progress and prospects: immune responses to viral vectors** S Nayak, RW Herzog *Gene Therapy* (2009-11-12) <https://doi.org/ctbtwq> DOI: [10.1038/gt.2009.148](https://doi.org/10.1038/gt.2009.148) · PMID: [19907498](https://www.ncbi.nlm.nih.gov/pubmed/19907498) · PMCID: [PMC3044498](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3044498)

89. **Developments in Viral Vector-Based Vaccines** Takehiro Ura, Kenji Okuda, Masaru Shimada *Vaccines* (2014-07-29) <https://doi.org/gcfnx9> DOI: [10.3390/vaccines2030624](https://doi.org/10.3390/vaccines2030624) · PMID: [26344749](https://www.ncbi.nlm.nih.gov/pubmed/26344749) · PMCID: [PMC4494222](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4494222)

90. **Development and Applications of Viral Vectored Vaccines to Combat Zoonotic and Emerging Public Health Threats** Sophia M Vrba, Natalie M Kirk, Morgan E Brisse, Yuying Liang, Hinh Ly *Vaccines* (2020-11-13) <https://doi.org/gh23ww> DOI: [10.3390/vaccines8040680](https://doi.org/10.3390/vaccines8040680) · PMID: [33202961](https://www.ncbi.nlm.nih.gov/pubmed/33202961) · PMCID: [PMC7712223](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7712223)

91. **Viral Vector Malaria Vaccines Induce High-Level T Cell and Antibody Responses in West African Children and Infants** Carly M Bliss, Abdoulie Drammeh, Georgina Bowyer, Guillaume S Sanou, Ya Jankey Jagne, Oumarou Ouedraogo, Nick J Edwards, Casimir Tarama, Nicolas Ouedraogo, Mireille Ouedraogo, … Katie J Ewer *Molecular Therapy* (2017-02) <https://doi.org/f9xwv3> DOI: [10.1016/j.ymthe.2016.11.003](https://doi.org/10.1016/j.ymthe.2016.11.003) · PMID: [28153101](https://www.ncbi.nlm.nih.gov/pubmed/28153101) · PMCID: [PMC5368405](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5368405)

92. **Viral vectors for malaria vaccine development** Shengqiang Li, Emily Locke, Joseph Bruder, David Clarke, Denise L Doolan, Menzo JE Havenga, Adrian VS Hill, Peter Liljestrom, Thomas P Monath, Hussein Y Naim, … Filip Dubovsky *Vaccine* (2007-03) <https://doi.org/fh9fn6> DOI: [10.1016/j.vaccine.2006.07.035](https://doi.org/10.1016/j.vaccine.2006.07.035) · PMID: [16914237](https://www.ncbi.nlm.nih.gov/pubmed/16914237) · PMCID: [PMC7131149](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7131149)

93. **Chimpanzee Adenovirus Vector Ebola Vaccine** Julie E Ledgerwood, Adam D DeZure, Daphne A Stanley, Emily E Coates, Laura Novik, Mary E Enama, Nina M Berkowitz, Zonghui Hu, Gyan Joshi, Aurélie Ploquin, … Barney S Graham *New England Journal of Medicine* (2017-03-09) <https://doi.org/xdr> DOI: [10.1056/nejmoa1410863](https://doi.org/10.1056/nejmoa1410863) · PMID: [25426834](https://www.ncbi.nlm.nih.gov/pubmed/25426834)

94. **Recombinant Vesicular Stomatitis Virus–Based Vaccines Against Ebola and Marburg Virus Infections** Thomas W Geisbert, Heinz Feldmann *The Journal of Infectious Diseases* (2011-11) <https://doi.org/fcvgxq> DOI: [10.1093/infdis/jir349](https://doi.org/10.1093/infdis/jir349) · PMID: [21987744](https://www.ncbi.nlm.nih.gov/pubmed/21987744) · PMCID: [PMC3218670](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3218670)

95. **Ebola virus vaccines: an overview of current approaches** Andrea Marzi, Heinz Feldmann *Expert Review of Vaccines* (2014-02-27) <https://doi.org/f52bn6> DOI: [10.1586/14760584.2014.885841](https://doi.org/10.1586/14760584.2014.885841) · PMID: [24575870](https://www.ncbi.nlm.nih.gov/pubmed/24575870) · PMCID: [PMC4785864](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4785864)

96. **Development of replication-competent viral vectors for HIV vaccine delivery** Christopher L Parks, Louis J Picker, CRichter King *Current Opinion in HIV and AIDS* (2013-09) <https://doi.org/f5b5qm> DOI: [10.1097/coh.0b013e328363d389](https://doi.org/10.1097/coh.0b013e328363d389) · PMID: [23925000](https://www.ncbi.nlm.nih.gov/pubmed/23925000) · PMCID: [PMC4040527](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4040527)

97. **Different HIV pox viral vector-based vaccines and adjuvants can induce unique antigen presenting cells that modulate CD8 T cell avidity** Shubhanshi Trivedi, Ronald J Jackson, Charani Ranasinghe *Virology* (2014-11) <https://doi.org/f6ngrk> DOI: [10.1016/j.virol.2014.09.004](https://doi.org/10.1016/j.virol.2014.09.004) · PMID: [25261870](https://www.ncbi.nlm.nih.gov/pubmed/25261870)

98. **Comparative evaluation of two severe acute respiratory syndrome (SARS) vaccine candidates in mice challenged with SARS coronavirus** Raymond H See, Alexander N Zakhartchouk, Martin Petric, David J Lawrence, Catherine PY Mok, Robert J Hogan, Thomas Rowe, Lois A Zitzow, Karuna P Karunakaran, Mary M Hitt, … BBrett Finlay *Journal of General Virology* (2006-03-01) <https://doi.org/fm9v5c> DOI: [10.1099/vir.0.81579-0](https://doi.org/10.1099/vir.0.81579-0) · PMID: [16476986](https://www.ncbi.nlm.nih.gov/pubmed/16476986)

99. **Severe acute respiratory syndrome vaccine efficacy in ferrets: whole killed virus and adenovirus-vectored vaccines** Raymond H See, Martin Petric, David J Lawrence, Catherine PY Mok, Thomas Rowe, Lois A Zitzow, Karuna P Karunakaran, Thomas G Voss, Robert C Brunham, Jack Gauldie, … Rachel L Roper *Journal of General Virology* (2008-09-01) <https://doi.org/c5wc6w> DOI: [10.1099/vir.0.2008/001891-0](https://doi.org/10.1099/vir.0.2008/001891-0) · PMID: [18753223](https://www.ncbi.nlm.nih.gov/pubmed/18753223)

100. **Update with the development of Ebola vaccines and implications of emerging evidence to inform future policy recommendations** Hoi Ting Yeung *World Health Organization SAGE meeting background* (2018-09-19) <https://www.who.int/immunization/sage/meetings/2018/october/2_Ebola_SAGE2018Oct_BgDoc_20180919.pdf>

101. **ChAdOx1 and MVA based vaccine candidates against MERS-CoV elicit neutralising antibodies and cellular immune responses in mice** Naif Khalaf Alharbi, Eriko Padron-Regalado, Craig P Thompson, Alexandra Kupke, Daniel Wells, Megan A Sloan, Keith Grehan, Nigel Temperton, Teresa Lambe, George Warimwe, … Sarah C Gilbert *Vaccine* (2017-06) <https://doi.org/gbms8z> DOI: [10.1016/j.vaccine.2017.05.032](https://doi.org/10.1016/j.vaccine.2017.05.032) · PMID: [28579232](https://www.ncbi.nlm.nih.gov/pubmed/28579232) · PMCID: [PMC5516308](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5516308)

102. **A single dose of ChAdOx1 MERS provides protective immunity in rhesus macaques** Neeltje van Doremalen, Elaine Haddock, Friederike Feldmann, Kimberly Meade-White, Trenton Bushmaker, Robert J Fischer, Atsushi Okumura, Patrick W Hanley, Greg Saturday, Nick J Edwards, … Vincent J Munster *Science Advances* (2020-06) <https://doi.org/gjkthv> DOI: [10.1126/sciadv.aba8399](https://doi.org/10.1126/sciadv.aba8399) · PMID: [32577525](https://www.ncbi.nlm.nih.gov/pubmed/32577525) · PMCID: [PMC7286676](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7286676)

103. **Safety and immunogenicity of a candidate Middle East respiratory syndrome coronavirus viral-vectored vaccine: a dose-escalation, open-label, non-randomised, uncontrolled, phase 1 trial** Pedro M Folegatti, Mustapha Bittaye, Amy Flaxman, Fernando Ramos Lopez, Duncan Bellamy, Alexandra Kupke, Catherine Mair, Rebecca Makinson, Jonathan Sheridan, Cornelius Rohde, … Sarah Gilbert *The Lancet Infectious Diseases* (2020-07) <https://doi.org/ggtxgp> DOI: [10.1016/s1473-3099(20)30160-2](https://doi.org/10.1016/s1473-3099(20)30160-2) · PMID: [32325038](https://www.ncbi.nlm.nih.gov/pubmed/32325038) · PMCID: [PMC7172901](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7172901)

104. **ChAdOx1 nCoV-19 vaccine prevents SARS-CoV-2 pneumonia in rhesus macaques** Neeltje van Doremalen, Teresa Lambe, Alexandra Spencer, Sandra Belij-Rammerstorfer, Jyothi N Purushotham, Julia R Port, Victoria A Avanzato, Trenton Bushmaker, Amy Flaxman, Marta Ulaszewska, … Vincent J Munster *Nature* (2020-07-30) <https://doi.org/gg67jr> DOI: [10.1038/s41586-020-2608-y](https://doi.org/10.1038/s41586-020-2608-y) · PMID: [32731258](https://www.ncbi.nlm.nih.gov/pubmed/32731258)

105. **Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial** Pedro M Folegatti, Katie J Ewer, Parvinder K Aley, Brian Angus, Stephan Becker, Sandra Belij-Rammerstorfer, Duncan Bellamy, Sagida Bibi, Mustapha Bittaye, Elizabeth A Clutterbuck, … Yasmine Yau *The Lancet* (2020-08) <https://doi.org/gg5gwk> DOI: [10.1016/s0140-6736(20)31604-4](https://doi.org/10.1016/s0140-6736(20)31604-4) · PMID: [32702298](https://www.ncbi.nlm.nih.gov/pubmed/32702298) · PMCID: [PMC7445431](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7445431)

106. **AstraZeneca’s COVID-19 vaccine authorised for emergency supply in the UK** <https://www.astrazeneca.com/media-centre/press-releases/2020/astrazenecas-covid-19-vaccine-authorised-in-uk.html>

107. **The Russian vaccine for COVID-19** Talha Khan Burki *The Lancet Respiratory Medicine* (2020-11) <https://doi.org/ft7j> DOI: [10.1016/s2213-2600(20)30402-1](https://doi.org/10.1016/s2213-2600(20)30402-1) · PMID: [32896274](https://www.ncbi.nlm.nih.gov/pubmed/32896274) · PMCID: [PMC7837053](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7837053)

108. **Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia** Denis Y Logunov, Inna V Dolzhikova, Olga V Zubkova, Amir I Tukhvatulin, Dmitry V Shcheblyakov, Alina S Dzharullaeva, Daria M Grousova, Alina S Erokhova, Anna V Kovyrshina, Andrei G Botikov, … Alexander L Gintsburg *The Lancet* (2020-09) <https://doi.org/gg96hq> DOI: [10.1016/s0140-6736(20)31866-3](https://doi.org/10.1016/s0140-6736(20)31866-3) · PMID: [32896291](https://www.ncbi.nlm.nih.gov/pubmed/32896291) · PMCID: [PMC7471804](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7471804)

109. **Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia** Denis Y Logunov, Inna V Dolzhikova, Dmitry V Shcheblyakov, Amir I Tukhvatulin, Olga V Zubkova, Alina S Dzharullaeva, Anna V Kovyrshina, Nadezhda L Lubenets, Daria M Grousova, Alina S Erokhova, … Alexander L Gintsburg *The Lancet* (2021-02) <https://doi.org/ghxj4g> DOI: [10.1016/s0140-6736(21)00234-8](https://doi.org/10.1016/s0140-6736(21)00234-8) · PMID: [33545094](https://www.ncbi.nlm.nih.gov/pubmed/33545094) · PMCID: [PMC7852454](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7852454)

110. **1.5 million people have received Sputnik V vaccine, Russia says** The Brussels Times (2021-01-11) <https://www.brusselstimes.com/news-contents/world/149039/1-5-million-people-have-received-sputnik-v-vaccine-russia-says-russian-direct-investment-fund-mikhail-murashko/>

111. **Hungary becomes first EU country to deploy Russia's COVID-19 vaccine** Michael Daventry *euronews* (2021-02-12) <https://www.euronews.com/2021/02/12/hungary-to-begin-using-russia-s-sputnik-v-vaccine-today>

112. **San Marino buys Russia's Sputnik V after EU vaccine delivery delays** euronews (2021-02-24) <https://www.euronews.com/2021/02/24/san-marino-buys-russia-s-sputnik-v-after-eu-vaccine-delivery-delays>

113. **Belarus Starts Coronavirus Vaccination With Sputnik V** AFP *The Moscow Times* (2020-12-29) <https://www.themoscowtimes.com/2020/12/29/belarus-starts-coronavirus-vaccination-with-sputnik-v-a72512>

114. **Russia's coronavirus vaccine is alluring for Eastern Europe, creating a headache for the EU** Holly Ellyatt *CNBC* (2021-03-02) <https://www.cnbc.com/2021/03/02/russias-sputnik-vaccine-is-luring-eastern-europe-worrying-the-eu.html>

115. **Operation Warp Speed: Accelerated COVID-19 Vaccine Development Status and Efforts to Address Manufacturing Challenges** USGovernment Accountability Office <https://www.gao.gov/products/gao-21-319>

116. **Johnson & Johnson Announces a Lead Vaccine Candidate for COVID-19; Landmark New Partnership with U.S. Department of Health & Human Services; and Commitment to Supply One Billion Vaccines Worldwide for Emergency Pandemic Use | Johnson & Johnson** Content Lab U.S. <https://www.jnj.com/johnson-johnson-announces-a-lead-vaccine-candidate-for-covid-19-landmark-new-partnership-with-u-s-department-of-health-human-services-and-commitment-to-supply-one-billion-vaccines-worldwide-for-emergency-pandemic-use>

117. **Interim Results of a Phase 1–2a Trial of Ad26.COV2.S Covid-19 Vaccine** Jerald Sadoff, Mathieu Le Gars, Georgi Shukarev, Dirk Heerwegh, Carla Truyers, Anne M de Groot, Jeroen Stoop, Sarah Tete, Wim Van Damme, Isabel Leroux-Roels, … Hanneke Schuitemaker *New England Journal of Medicine* (2021-05-13) <https://doi.org/fqnt> DOI: [10.1056/nejmoa2034201](https://doi.org/10.1056/nejmoa2034201) · PMID: [33440088](https://www.ncbi.nlm.nih.gov/pubmed/33440088) · PMCID: [PMC7821985](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7821985)

118. **Ad26 vector-based COVID-19 vaccine encoding a prefusion-stabilized SARS-CoV-2 Spike immunogen induces potent humoral and cellular immune responses** Rinke Bos, Lucy Rutten, Joan EM van der Lubbe, Mark JG Bakkers, Gijs Hardenberg, Frank Wegmann, David Zuijdgeest, Adriaan H de Wilde, Annemart Koornneef, Annemiek Verwilligen, … Hanneke Schuitemaker *npj Vaccines* (2020-09-28) <https://doi.org/ghjkr8> DOI: [10.1038/s41541-020-00243-x](https://doi.org/10.1038/s41541-020-00243-x) · PMID: [33083026](https://www.ncbi.nlm.nih.gov/pubmed/33083026) · PMCID: [PMC7522255](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7522255)

119. **Single-shot Ad26 vaccine protects against SARS-CoV-2 in rhesus macaques** Noe B Mercado, Roland Zahn, Frank Wegmann, Carolin Loos, Abishek Chandrashekar, Jingyou Yu, Jinyan Liu, Lauren Peter, Katherine McMahan, Lisa H Tostanoski, … Dan H Barouch *Nature* (2020-07-30) <https://doi.org/d5d4> DOI: [10.1038/s41586-020-2607-z](https://doi.org/10.1038/s41586-020-2607-z) · PMID: [32731257](https://www.ncbi.nlm.nih.gov/pubmed/32731257) · PMCID: [PMC7581548](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7581548)

120. **Ad26 vaccine protects against SARS-CoV-2 severe clinical disease in hamsters** Lisa H Tostanoski, Frank Wegmann, Amanda J Martinot, Carolin Loos, Katherine McMahan, Noe B Mercado, Jingyou Yu, Chi N Chan, Stephen Bondoc, Carly E Starke, … Dan H Barouch *Nature Medicine* (2020-09-03) <https://doi.org/gjhgd2> DOI: [10.1038/s41591-020-1070-6](https://doi.org/10.1038/s41591-020-1070-6) · PMID: [32884153](https://www.ncbi.nlm.nih.gov/pubmed/32884153) · PMCID: [PMC7671939](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7671939)

121. **Immunogenicity and protective efficacy of one- and two-dose regimens of the Ad26.COV2.S COVID-19 vaccine candidate in adult and aged rhesus macaques** Laura Solforosi, Harmjan Kuipers, Sietske KRosendahl Huber, Joan EM van der Lubbe, Liesbeth Dekking, Dominika N Czapska-Casey, Ana Izquierdo Gil, Miranda RM Baert, Joke Drijver, Joost Vaneman, … Roland C Zahn *Cold Spring Harbor Laboratory* (2021-01-04) <https://doi.org/ghwzk9> DOI: [10.1101/2020.11.17.368258](https://doi.org/10.1101/2020.11.17.368258)

122. **SARS-CoV-2 binding and neutralizing antibody levels after vaccination with Ad26.COV2.S predict durable protection in rhesus macaques** Ramon Roozendaal, Laura Solforosi, Daniel Stieh, Jan Serroyen, Roel Straetemans, Frank Wegmann, Sietske K Rosendahl Huber, Joan EM van der Lubbe, Jenny Hendriks, Mathieu le Gars, … Roland Zahn *Cold Spring Harbor Laboratory* (2021-01-30) <https://doi.org/gjhgd4> DOI: [10.1101/2021.01.30.428921](https://doi.org/10.1101/2021.01.30.428921)

123. **Janssen Investigational COVID-19 Vaccine: Interim Analysis of Phase 3 Clinical Data Released** National Institutes of Health (NIH) (2021-01-29) <https://www.nih.gov/news-events/news-releases/janssen-investigational-covid-19-vaccine-interim-analysis-phase-3-clinical-data-released>

124. **Johnson & Johnson Announces Single-Shot Janssen COVID-19 Vaccine Candidate Met Primary Endpoints in Interim Analysis of its Phase 3 ENSEMBLE Trial** Janssen (2021-01-29) <https://www.janssen.com/emea/sites/www_janssen_com_emea/files/johnson_johnson_announces_single-shot_janssen_covid-19_vaccine_candidate_met_primary_endpoints_in_interim_analysis_of_its_phase_3_ensemble_trial.pdf>

125. **B.1.351 report** <https://cov-lineages.org/global_report_B.1.351.html>

126. **Structural features of coronavirus SARS-CoV-2 spike protein: Targets for vaccination** Ariane Sternberg, Cord Naujokat *Life Sciences* (2020-09) <https://doi.org/gg4cmp> DOI: [10.1016/j.lfs.2020.118056](https://doi.org/10.1016/j.lfs.2020.118056) · PMID: [32645344](https://www.ncbi.nlm.nih.gov/pubmed/32645344) · PMCID: [PMC7336130](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7336130)

127. **Structure, Function, and Evolution of Coronavirus Spike Proteins** Fang Li *Annual Review of Virology* (2016-09-29) <https://doi.org/ggr7gv> DOI: [10.1146/annurev-virology-110615-042301](https://doi.org/10.1146/annurev-virology-110615-042301) · PMID: [27578435](https://www.ncbi.nlm.nih.gov/pubmed/27578435) · PMCID: [PMC5457962](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5457962)

128. **Pre-fusion structure of a human coronavirus spike protein** Robert N Kirchdoerfer, Christopher A Cottrell, Nianshuang Wang, Jesper Pallesen, Hadi M Yassine, Hannah L Turner, Kizzmekia S Corbett, Barney S Graham, Jason S McLellan, Andrew B Ward *Nature* (2016-03-02) <https://doi.org/f8b8zb> DOI: [10.1038/nature17200](https://doi.org/10.1038/nature17200) · PMID: [26935699](https://www.ncbi.nlm.nih.gov/pubmed/26935699) · PMCID: [PMC4860016](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4860016)

129. **Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein** Alexandra C Walls, Young-Jun Park, MAlejandra Tortorici, Abigail Wall, Andrew T McGuire, David Veesler *Cell* (2020-04) <https://doi.org/dpvh> DOI: [10.1016/j.cell.2020.02.058](https://doi.org/10.1016/j.cell.2020.02.058) · PMID: [32155444](https://www.ncbi.nlm.nih.gov/pubmed/32155444) · PMCID: [PMC7102599](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102599)

130. **The Architecture of Inactivated SARS-CoV-2 with Postfusion Spikes Revealed by Cryo-EM and Cryo-ET** Chuang Liu, Luiza Mendonça, Yang Yang, Yuanzhu Gao, Chenguang Shen, Jiwei Liu, Tao Ni, Bin Ju, Congcong Liu, Xian Tang, … Peijun Zhang *Structure* (2020-11) <https://doi.org/ghhwtg> DOI: [10.1016/j.str.2020.10.001](https://doi.org/10.1016/j.str.2020.10.001) · PMID: [33058760](https://www.ncbi.nlm.nih.gov/pubmed/33058760) · PMCID: [PMC7557167](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7557167)

131. **Structures and distributions of SARS-CoV-2 spike proteins on intact virions** Zunlong Ke, Joaquin Oton, Kun Qu, Mirko Cortese, Vojtech Zila, Lesley McKeane, Takanori Nakane, Jasenko Zivanov, Christopher J Neufeldt, Berati Cerikan, … John AG Briggs *Nature* (2020-08-17) <https://doi.org/d6sf> DOI: [10.1038/s41586-020-2665-2](https://doi.org/10.1038/s41586-020-2665-2) · PMID: [32805734](https://www.ncbi.nlm.nih.gov/pubmed/32805734) · PMCID: [PMC7116492](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7116492)

132. **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* (2017-08-29) <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)

133. **Mechanisms of Coronavirus Cell Entry Mediated by the Viral Spike Protein** Sandrine Belouzard, Jean K Millet, Beth N Licitra, Gary R Whittaker *Viruses* (2012-06-20) <https://doi.org/gbbktb> DOI: [10.3390/v4061011](https://doi.org/10.3390/v4061011) · PMID: [22816037](https://www.ncbi.nlm.nih.gov/pubmed/22816037) · PMCID: [PMC3397359](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3397359)

134. **Phylogenetic Analysis and Structural Modeling of SARS-CoV-2 Spike Protein Reveals an Evolutionary Distinct and Proteolytically Sensitive Activation Loop** Javier A Jaimes, Nicole M André, Joshua S Chappie, Jean K Millet, Gary R Whittaker *Journal of Molecular Biology* (2020-05) <https://doi.org/ggtxhr> DOI: [10.1016/j.jmb.2020.04.009](https://doi.org/10.1016/j.jmb.2020.04.009) · PMID: [32320687](https://www.ncbi.nlm.nih.gov/pubmed/32320687) · PMCID: [PMC7166309](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7166309)

135. **Structure-based design of prefusion-stabilized SARS-CoV-2 spikes** Ching-Lin Hsieh, Jory A Goldsmith, Jeffrey M Schaub, Andrea M DiVenere, Hung-Che Kuo, Kamyab Javanmardi, Kevin C Le, Daniel Wrapp, Alison G Lee, Yutong Liu, … Jason S McLellan *Science* (2020-09-18) <https://doi.org/gg8k5r> DOI: [10.1126/science.abd0826](https://doi.org/10.1126/science.abd0826) · PMID: [32703906](https://www.ncbi.nlm.nih.gov/pubmed/32703906) · PMCID: [PMC7402631](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7402631)

136. **Induction of virus-specific cytotoxic T lymphocytesin vivo by liposome-entrapped mRNA** Frédéric Martinon, Sivadasan Krishnan, Gerlinde Lenzen, Rémy Magné, Elisabeth Gomard, Jean-Gérard Guillet, Jean-Paul Lévy, Pierre Meulien *European Journal of Immunology* (1993-07) <https://doi.org/b6jb3z> DOI: [10.1002/eji.1830230749](https://doi.org/10.1002/eji.1830230749) · PMID: [8325342](https://www.ncbi.nlm.nih.gov/pubmed/8325342)

137. **mRNA vaccine delivery using lipid nanoparticles** Andreas M Reichmuth, Matthias A Oberli, Ana Jaklenec, Robert Langer, Daniel Blankschtein *Therapeutic Delivery* (2016-05) <https://doi.org/f8xfzc> DOI: [10.4155/tde-2016-0006](https://doi.org/10.4155/tde-2016-0006) · PMID: [27075952](https://www.ncbi.nlm.nih.gov/pubmed/27075952) · PMCID: [PMC5439223](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5439223)

138. **Mechanism of action of mRNA-based vaccines** Carlo Iavarone, Derek T O’hagan, Dong Yu, Nicolas F Delahaye, Jeffrey B Ulmer *Expert Review of Vaccines* (2017-07-28) <https://doi.org/ggsnm6> DOI: [10.1080/14760584.2017.1355245](https://doi.org/10.1080/14760584.2017.1355245) · PMID: [28701102](https://www.ncbi.nlm.nih.gov/pubmed/28701102)

139. **RNA vaccines: an introduction** PHG Foundation <https://www.phgfoundation.org/briefing/rna-vaccines>

140. **T Follicular Helper Cell Differentiation, Function, and Roles in Disease** Shane Crotty *Immunity* (2014-10) <https://doi.org/ggsp64> DOI: [10.1016/j.immuni.2014.10.004](https://doi.org/10.1016/j.immuni.2014.10.004) · PMID: [25367570](https://www.ncbi.nlm.nih.gov/pubmed/25367570) · PMCID: [PMC4223692](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4223692)

141. **SARS-CoV-2 Vaccines: Status Report** Fatima Amanat, Florian Krammer *Immunity* (2020-04) <https://doi.org/ggrdj4> DOI: [10.1016/j.immuni.2020.03.007](https://doi.org/10.1016/j.immuni.2020.03.007) · PMID: [32259480](https://www.ncbi.nlm.nih.gov/pubmed/32259480) · PMCID: [PMC7136867](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7136867)

142. **Study in Healthy Adults to Evaluate Gene Activation After Vaccination With GlaxoSmithKline (GSK) Biologicals' Candidate Tuberculosis (TB) Vaccine GSK 692342 - Full Text View - ClinicalTrials.gov** <https://clinicaltrials.gov/ct2/show/NCT01669096>

143. **Nucleoside-modified mRNA immunization elicits influenza virus hemagglutinin stalk-specific antibodies** Norbert Pardi, Kaela Parkhouse, Ericka Kirkpatrick, Meagan McMahon, Seth J Zost, Barbara L Mui, Ying K Tam, Katalin Karikó, Christopher J Barbosa, Thomas D Madden, … Drew Weissman *Nature Communications* (2018-08-22) <https://doi.org/gd49qt> DOI: [10.1038/s41467-018-05482-0](https://doi.org/10.1038/s41467-018-05482-0) · PMID: [30135514](https://www.ncbi.nlm.nih.gov/pubmed/30135514) · PMCID: [PMC6105651](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6105651)

144. **Cell specific delivery of modified mRNA expressing therapeutic proteins to leukocytes** Nuphar Veiga, Meir Goldsmith, Yasmin Granot, Daniel Rosenblum, Niels Dammes, Ranit Kedmi, Srinivas Ramishetti, Dan Peer *Nature Communications* (2018-10-29) <https://doi.org/gfmcrt> DOI: [10.1038/s41467-018-06936-1](https://doi.org/10.1038/s41467-018-06936-1) · PMID: [30374059](https://www.ncbi.nlm.nih.gov/pubmed/30374059) · PMCID: [PMC6206083](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6206083)

145. **Immunology of COVID-19: Current State of the Science** Nicolas Vabret, Graham J Britton, Conor Gruber, Samarth Hegde, Joel Kim, Maria Kuksin, Rachel Levantovsky, Louise Malle, Alvaro Moreira, Matthew D Park, … Uri Laserson *Immunity* (2020-06) <https://doi.org/ggt54g> DOI: [10.1016/j.immuni.2020.05.002](https://doi.org/10.1016/j.immuni.2020.05.002) · PMID: [32505227](https://www.ncbi.nlm.nih.gov/pubmed/32505227) · PMCID: [PMC7200337](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7200337)

146. **Synthetic Chemically Modified mRNA (modRNA): Toward a New Technology Platform for Cardiovascular Biology and Medicine** KR Chien, L Zangi, KO Lui *Cold Spring Harbor Perspectives in Medicine* (2014-10-09) <https://doi.org/f3pvsr> DOI: [10.1101/cshperspect.a014035](https://doi.org/10.1101/cshperspect.a014035) · PMID: [25301935](https://www.ncbi.nlm.nih.gov/pubmed/25301935) · PMCID: [PMC4292072](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4292072)

147. **Pfizer and BioNTech Announce Early Positive Data from an Ongoing Phase 1/2 study of mRNA-based Vaccine Candidate Against SARS-CoV-2 | Pfizer** <https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-early-positive-data-ongoing-0>

148. **Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine** Fernando P Polack, Stephen J Thomas, Nicholas Kitchin, Judith Absalon, Alejandra Gurtman, Stephen Lockhart, John L Perez, Gonzalo Pérez Marc, Edson D Moreira, Cristiano Zerbini, … William C Gruber *New England Journal of Medicine* (2020-12-31) <https://doi.org/ghn625> DOI: [10.1056/nejmoa2034577](https://doi.org/10.1056/nejmoa2034577) · PMID: [33301246](https://www.ncbi.nlm.nih.gov/pubmed/33301246) · PMCID: [PMC7745181](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7745181)

149. **Phase I, Open-Label, Dose-Ranging Study of the Safety and Immunogenicity of 2019-nCoV Vaccine (mRNA-1273) in Healthy Adults** National Institute of Allergy and Infectious Diseases (NIAID) *clinicaltrials.gov* (2020-12-17) <https://clinicaltrials.gov/ct2/show/NCT04283461>

150. **Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine** Lindsey R Baden, Hana M El Sahly, Brandon Essink, Karen Kotloff, Sharon Frey, Rick Novak, David Diemert, Stephen A Spector, Nadine Rouphael, CBuddy Creech, … Tal Zaks *New England Journal of Medicine* (2020-12-30) <https://doi.org/ghrg8m> DOI: [10.1056/nejmoa2035389](https://doi.org/10.1056/nejmoa2035389) · PMID: [33378609](https://www.ncbi.nlm.nih.gov/pubmed/33378609) · PMCID: [PMC7787219](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7787219)

151. **FDA Takes Key Action in Fight Against COVID-19 By Issuing Emergency Use Authorization for First COVID-19 Vaccine** Office of the Commissioner *FDA* (2020-12-14) <https://www.fda.gov/news-events/press-announcements/fda-takes-key-action-fight-against-covid-19-issuing-emergency-use-authorization-first-covid-19>

152. **The Advisory Committee on Immunization Practices’ Interim Recommendation for Use of Moderna COVID-19 Vaccine — United States, December 2020** Sara E Oliver *MMWR. Morbidity and Mortality Weekly Report* (2021) <https://www.cdc.gov/mmwr/volumes/69/wr/mm695152e1.htm> DOI: [10.15585/mmwr.mm695152e1](https://doi.org/10.15585/mmwr.mm695152e1)

153. **Safety and immunogenicity of a novel human Enterovirus 71 (EV71) vaccine: A randomized, placebo-controlled, double-blind, Phase I clinical trial** Yan-Ping Li, Zheng-Lun Liang, Qiang Gao, Li-Rong Huang, Qun-Ying Mao, Shu-Qun Wen, Yan Liu, Wei-Dong Yin, Rong-Cheng Li, Jun-Zhi Wang *Vaccine* (2012-05) <https://doi.org/gh7tjn> DOI: [10.1016/j.vaccine.2012.03.010](https://doi.org/10.1016/j.vaccine.2012.03.010) · PMID: [22426327](https://www.ncbi.nlm.nih.gov/pubmed/22426327)

154. **A Snapshot of the Global Race for Vaccines Targeting SARS-CoV-2 and the COVID-19 Pandemic** Colin D Funk, Craig Laferrière, Ali Ardakani *Frontiers in Pharmacology* (2020-06-19) <https://doi.org/gg4hxd> DOI: [10.3389/fphar.2020.00937](https://doi.org/10.3389/fphar.2020.00937) · PMID: [32636754](https://www.ncbi.nlm.nih.gov/pubmed/32636754) · PMCID: [PMC7317023](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7317023)

155. **Moderna’s COVID-19 Vaccine Candidate Meets its Primary Efficacy Endpoint in the First Interim Analysis of the Phase 3 COVE Study | Moderna, Inc.** <https://investors.modernatx.com/news-releases/news-release-details/modernas-covid-19-vaccine-candidate-meets-its-primary-efficacy/>

156. **Vaccines and Related Biological Products Advisory Committee December 17, 2020 Meeting Announcement - 12/17/2020 - 12/17/2020** FDA (2021-01-27) <https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-december-17-2020-meeting-announcement>

157.  **Vaccines and Related Biological Products Advisory Committee December 17, 2020 Meeting Briefing Document - FDA**  FDA/CBER (2020-12-15) <https://www.fda.gov/media/144434/download>

158. **Moderna Has Completed Case Accrual for First Planned Interim Analysis of its mRNA Vaccine Against COVID-19 (mRNA-1273) | Moderna, Inc.** <https://investors.modernatx.com/news-releases/news-release-details/moderna-has-completed-case-accrual-first-planned-interim/>

159.  **Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials**  CBER (2018-10-08) <https://www.fda.gov/media/73679/download>

160. **Health Canada Authorizes Moderna COVID-19 Vaccine in Canada | Moderna, Inc.** <https://investors.modernatx.com/news-releases/news-release-details/health-canada-authorizes-moderna-covid-19-vaccine-canada/>

161. **EMA recommends COVID-19 Vaccine Moderna for authorisation in the EU** Daniel GLANVILLE *European Medicines Agency* (2021-01-06) <https://www.ema.europa.eu/en/news/ema-recommends-covid-19-vaccine-moderna-authorisation-eu>

162. **Pfizer and BioNTech Announce Vaccine Candidate Against COVID-19 Achieved Success in First Interim Analysis from Phase 3 Study | Pfizer** <https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-vaccine-candidate-against>

163. **Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults** Mark J Mulligan, Kirsten E Lyke, Nicholas Kitchin, Judith Absalon, Alejandra Gurtman, Stephen Lockhart, Kathleen Neuzil, Vanessa Raabe, Ruth Bailey, Kena A Swanson, … Kathrin U Jansen *Nature* (2020-08-12) <https://doi.org/gg7ww9> DOI: [10.1038/s41586-020-2639-4](https://doi.org/10.1038/s41586-020-2639-4) · PMID: [32785213](https://www.ncbi.nlm.nih.gov/pubmed/32785213)

164. **COVID-19 vaccine BNT162b1 elicits human antibody and TH1 T cell responses** Ugur Sahin, Alexander Muik, Evelyna Derhovanessian, Isabel Vogler, Lena M Kranz, Mathias Vormehr, Alina Baum, Kristen Pascal, Jasmin Quandt, Daniel Maurus, … Özlem Türeci *Nature* (2020-09-30) <https://doi.org/ghfmb2> DOI: [10.1038/s41586-020-2814-7](https://doi.org/10.1038/s41586-020-2814-7) · PMID: [32998157](https://www.ncbi.nlm.nih.gov/pubmed/32998157)

165. **Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates** Edward E Walsh, Robert W Frenck, Ann R Falsey, Nicholas Kitchin, Judith Absalon, Alejandra Gurtman, Stephen Lockhart, Kathleen Neuzil, Mark J Mulligan, Ruth Bailey, … William C Gruber *New England Journal of Medicine* (2020-12-17) <https://doi.org/ghjktx> DOI: [10.1056/nejmoa2027906](https://doi.org/10.1056/nejmoa2027906) · PMID: [33053279](https://www.ncbi.nlm.nih.gov/pubmed/33053279) · PMCID: [PMC7583697](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7583697)

166. **Coronavirus COVID-19 Vaccine Update: Latest Developments | Pfizer** <https://www.pfizer.com/science/coronavirus/vaccine>

167. **Pfizer and BioNTech Conclude Phase 3 Study of COVID-19 Vaccine Candidate, Meeting All Primary Efficacy Endpoints | Pfizer** <https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-conclude-phase-3-study-covid-19-vaccine>

168. **Covid-19: UK approves Pfizer and BioNTech vaccine with rollout due to start next week** Elisabeth Mahase *BMJ* (2020-12-02) <https://doi.org/ghpnhg> DOI: [10.1136/bmj.m4714](https://doi.org/10.1136/bmj.m4714) · PMID: [33268330](https://www.ncbi.nlm.nih.gov/pubmed/33268330)

169. **Covid-19 vaccine: First person receives Pfizer jab in UK** BBC News (2020-12-08) <https://www.bbc.com/news/uk-55227325>

170. **Early effectiveness of COVID-19 vaccination with BNT162b2 mRNA vaccine and ChAdOx1 adenovirus vector vaccine on symptomatic disease, hospitalisations and mortality in older adults in England** Jamie Lopez Bernal, Nick Andrews, Charlotte Gower, Julia Stowe, Chris Robertson, Elise Tessier, Ruth Simmons, Simon Cottrell, Richard Roberts, Mark O’Doherty, … Mary Ramsay *Cold Spring Harbor Laboratory* (2021-03-02) <https://doi.org/gh63t4> DOI: [10.1101/2021.03.01.21252652](https://doi.org/10.1101/2021.03.01.21252652)

171. **The arrival of Sputnik V** Vijay Shankar Balakrishnan *The Lancet Infectious Diseases* (2020-10) <https://doi.org/ghs3sn> DOI: [10.1016/s1473-3099(20)30709-x](https://doi.org/10.1016/s1473-3099(20)30709-x) · PMID: [32979327](https://www.ncbi.nlm.nih.gov/pubmed/32979327) · PMCID: [PMC7511201](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7511201)

172. **Sputnik V COVID-19 vaccine candidate appears safe and effective** Ian Jones, Polly Roy *The Lancet* (2021-02) <https://doi.org/ghx7xz> DOI: [10.1016/s0140-6736(21)00191-4](https://doi.org/10.1016/s0140-6736(21)00191-4) · PMID: [33545098](https://www.ncbi.nlm.nih.gov/pubmed/33545098) · PMCID: [PMC7906719](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7906719)

173. **International seroepidemiology of adenovirus serotypes 5, 26, 35, and 48 in pediatric and adult populations** Dan H Barouch, Sandra V Kik, Gerrit J Weverling, Rebecca Dilan, Sharon L King, Lori F Maxfield, Sarah Clark, David Ng’ang’a, Kara L Brandariz, Peter Abbink, … Jaap Goudsmit *Vaccine* (2011-07) <https://doi.org/bmzpdx> DOI: [10.1016/j.vaccine.2011.05.025](https://doi.org/10.1016/j.vaccine.2011.05.025) · PMID: [21619905](https://www.ncbi.nlm.nih.gov/pubmed/21619905) · PMCID: [PMC3138857](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3138857)

174. **Oxford–AstraZeneca COVID-19 vaccine efficacy** Maria Deloria Knoll, Chizoba Wonodi *The Lancet* (2021-01) <https://doi.org/ghpghz> DOI: [10.1016/s0140-6736(20)32623-4](https://doi.org/10.1016/s0140-6736(20)32623-4) · PMID: [33306990](https://www.ncbi.nlm.nih.gov/pubmed/33306990) · PMCID: [PMC7832220](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7832220)

175. **Lead SARS-CoV-2 Candidate Vaccines: Expectations from Phase III Trials and Recommendations Post-Vaccine Approval** Ebenezer Tumban *Viruses* (2020-12-31) <https://doi.org/gh2z7h> DOI: [10.3390/v13010054](https://doi.org/10.3390/v13010054) · PMID: [33396343](https://www.ncbi.nlm.nih.gov/pubmed/33396343) · PMCID: [PMC7824305](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7824305)

176. **A dangerous rush for vaccines** HHolden Thorp *Science* (2020-08-21) <https://doi.org/gh2pwb> DOI: [10.1126/science.abe3147](https://doi.org/10.1126/science.abe3147) · PMID: [32792466](https://www.ncbi.nlm.nih.gov/pubmed/32792466)

177. **Scientists worry whether Russia's 'Sputnik V' coronavirus vaccine is safe and effective** Berkeley Lovelace Jr *CNBC* (2020-08-11) <https://www.cnbc.com/2020/08/11/scientists-worry-whether-russias-sputnik-v-coronavirus-vaccine-is-safe-and-effective.html>

178. **Russia’s claim of a successful COVID-19 vaccine doesn’t pass the ‘smell test,’ critics say** Jon Cohen *Science* (2020-11-11) <https://doi.org/gh2pwc> DOI: [10.1126/science.abf6791](https://doi.org/10.1126/science.abf6791)

179. **Russia announces positive COVID-vaccine results from controversial trial** Ewen Callaway *Nature* (2020-11-11) <https://doi.org/gh2pv9> DOI: [10.1038/d41586-020-03209-0](https://doi.org/10.1038/d41586-020-03209-0) · PMID: [33177689](https://www.ncbi.nlm.nih.gov/pubmed/33177689)

180. **Covid-19: Russian vaccine efficacy is 91.6%, show phase III trial results** Elisabeth Mahase *BMJ* (2021-02-02) <https://doi.org/gh2pwd> DOI: [10.1136/bmj.n309](https://doi.org/10.1136/bmj.n309) · PMID: [33531342](https://www.ncbi.nlm.nih.gov/pubmed/33531342)

181. **Russia cuts size of COVID-19 vaccine study, stops enrollment** ABC News *ABC News* <https://abcnews.go.com/Health/wireStory/russia-cuts-size-covid-19-vaccine-study-stops-74885458>

182. **About Vaccine** <https://sputnikvaccine.com/about-vaccine/>

183. **Active Surveillance of the Sputnik V Vaccine in Health Workers** Vanina Pagotto, Analia Ferloni, María Mercedes Soriano, Morena Díaz, Manuel Braguisnky Golde, María Isabel González, Valeria Asprea, Inés Staneloni, Gustavo Vidal, Martin Silveira, … Silvana Figar (2021-02-05) <https://www.medrxiv.org/content/10.1101/2021.02.03.21251071v1>

184. **UPDATE 1-Russia's Sputnik V vaccine found safe in India mid-stage trial -Dr.Reddy's** Reuters (2021-01-11) <https://www.reuters.com/article/health-coronavirus-india-vaccine-idUSL4N2JM2XA>

185. **Russian Direct Investment Fund** <https://rdif.ru/Eng_fullNews/6220/>

186. **A Phase II Open-label Study in Adults to Determine the Safety and Immunogenicity of AZD1222, a Non-replicating ChAdOx1 Vector Vaccine, Given in Combination With rAd26-S, Recombinant Adenovirus Type 26 Component of Gam-COVID-Vac Vaccine, for the Prevention of COVID 19** R-Pharm *clinicaltrials.gov* (2021-01-12) <https://clinicaltrials.gov/ct2/show/NCT04686773>

187. **The first registered COVID-19 vaccine** <https://sputnikvaccine.com/>

188. **Johnson & Johnson Initiates Pivotal Global Phase 3 Clinical Trial of Janssen’s COVID-19 Vaccine Candidate | Johnson & Johnson** Content Lab U.S. <https://www.jnj.com/johnson-johnson-initiates-pivotal-global-phase-3-clinical-trial-of-janssens-covid-19-vaccine-candidate>

189. **Low-Dose Ad26.COV2.S Protection Against SARS-CoV-2 Challenge in Rhesus Macaques** Xuan He, Abishek Chandrashekar, Roland Zahn, Frank Wegmann, Jingyou Yu, Noe B Mercado, Katherine McMahan, Amanda J Martinot, Cesar Piedra-Mora, Sidney Beecy, … Dan H Barouch *Cold Spring Harbor Laboratory* (2021-01-27) <https://doi.org/gjhgd3> DOI: [10.1101/2021.01.27.428380](https://doi.org/10.1101/2021.01.27.428380) · PMID: [33532782](https://www.ncbi.nlm.nih.gov/pubmed/33532782) · PMCID: [PMC7852276](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7852276)

190. **Safety and immunogenicity of the Ad26.COV2.S COVID-19 vaccine candidate: interim results of a phase 1/2a, double-blind, randomized, placebo-controlled trial** Jerald Sadoff, Mathieu Le Gars, Georgi Shukarev, Dirk Heerwegh, Carla Truyers, Anne Marit de Groot, Jeroen Stoop, Sarah Tete, Wim Van Damme, Isabel Leroux-Roels, … Hanneke Schuitemaker *Cold Spring Harbor Laboratory* (2020-09-25) <https://doi.org/ghjk2q> DOI: [10.1101/2020.09.23.20199604](https://doi.org/10.1101/2020.09.23.20199604)

191. **Immunogenicity of the Ad26.COV2.S Vaccine for COVID-19** Kathryn E Stephenson, Mathieu Le Gars, Jerald Sadoff, Anne Marit de Groot, Dirk Heerwegh, Carla Truyers, Caroline Atyeo, Carolin Loos, Abishek Chandrashekar, Katherine McMahan, … Dan H Barouch *JAMA* (2021-04-20) <https://doi.org/gjhgdz> DOI: [10.1001/jama.2021.3645](https://doi.org/10.1001/jama.2021.3645) · PMID: [33704352](https://www.ncbi.nlm.nih.gov/pubmed/33704352) · PMCID: [PMC7953339](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7953339)

192. **Correlates of protection against SARS-CoV-2 in rhesus macaques** Katherine McMahan, Jingyou Yu, Noe B Mercado, Carolin Loos, Lisa H Tostanoski, Abishek Chandrashekar, Jinyan Liu, Lauren Peter, Caroline Atyeo, Alex Zhu, … Dan H Barouch *Nature* (2020-12-04) <https://doi.org/fmjk> DOI: [10.1038/s41586-020-03041-6](https://doi.org/10.1038/s41586-020-03041-6) · PMID: [33276369](https://www.ncbi.nlm.nih.gov/pubmed/33276369) · PMCID: [PMC7906955](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7906955)

193. **A Randomized, Double-blind, Placebo-controlled Phase 3 Study to Assess the Efficacy and Safety of Ad26.COV2.S for the Prevention of SARS-CoV-2-mediated COVID-19 in Adults Aged 18 Years and Older** Janssen Vaccines & Prevention B.V. *clinicaltrials.gov* (2021-08-31) <https://clinicaltrials.gov/ct2/show/NCT04505722>

194. **Johnson & Johnson Prepares to Resume Phase 3 ENSEMBLE Trial of its Janssen COVID-19 Vaccine Candidate in the U.S. | Johnson & Johnson** Content Lab U.S. <https://www.jnj.com/our-company/johnson-johnson-prepares-to-resume-phase-3-ensemble-trial-of-its-janssen-covid-19-vaccine-candidate-in-the-us>

195. **B.1.1.7 report** <https://cov-lineages.org/global_report_B.1.1.7.html>

196. **Johnson & Johnson Initiates Second Global Phase 3 Clinical Trial of its Janssen COVID-19 Vaccine Candidate | Johnson & Johnson** Content Lab U.S. <https://www.jnj.com/johnson-johnson-initiates-second-global-phase-3-clinical-trial-of-its-janssen-covid-19-vaccine-candidate>

197. **Matrix-M™ adjuvant enhances immunogenicity of both protein- and modified vaccinia virus Ankara-based influenza vaccines in mice** Sofia E Magnusson, Arwen F Altenburg, Karin Lövgren Bengtsson, Fons Bosman, Rory D de Vries, Guus F Rimmelzwaan, Linda Stertman *Immunologic Research* (2018-03-28) <https://doi.org/gdd2fw> DOI: [10.1007/s12026-018-8991-x](https://doi.org/10.1007/s12026-018-8991-x) · PMID: [29594879](https://www.ncbi.nlm.nih.gov/pubmed/29594879) · PMCID: [PMC5899102](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5899102)

198. **Immune enhancing properties of the novel Matrix-M™ adjuvant leads to potentiated immune responses to an influenza vaccine in mice** Sofia E Magnusson, Jenny M Reimer, Karin H Karlsson, Lena Lilja, Karin Lövgren Bengtsson, Linda Stertman *Vaccine* (2013-03) <https://doi.org/f2ntg8> DOI: [10.1016/j.vaccine.2013.01.039](https://doi.org/10.1016/j.vaccine.2013.01.039) · PMID: [23384754](https://www.ncbi.nlm.nih.gov/pubmed/23384754)

199. **Intramuscular Matrix-M-adjuvanted virosomal H5N1 vaccine induces high frequencies of multifunctional Th1 CD4+ cells and strong antibody responses in mice** Abdullah S Madhun, Lars R Haaheim, Mona V Nilsen, Rebecca J Cox *Vaccine* (2009-12) <https://doi.org/d6cthn> DOI: [10.1016/j.vaccine.2009.09.044](https://doi.org/10.1016/j.vaccine.2009.09.044) · PMID: [19781678](https://www.ncbi.nlm.nih.gov/pubmed/19781678)

200. **Matrix-M adjuvanted virosomal H5N1 vaccine confers protection against lethal viral challenge in a murine model** Gabriel Pedersen, Diane Major, Sarah Roseby, John Wood, Abdullah S Madhun, Rebecca J Cox *Influenza and Other Respiratory Viruses* (2011-11) <https://doi.org/fbkc9w> DOI: [10.1111/j.1750-2659.2011.00256.x](https://doi.org/10.1111/j.1750-2659.2011.00256.x) · PMID: [21668670](https://www.ncbi.nlm.nih.gov/pubmed/21668670) · PMCID: [PMC5780659](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5780659)

201. **Evaluation of a virosomal H5N1 vaccine formulated with Matrix M™ adjuvant in a phase I clinical trial** Rebecca J Cox, Gabriel Pedersen, Abdullah S Madhun, Signe Svindland, Marianne Sævik, Lucy Breakwell, Katja Hoschler, Marieke Willemsen, Laura Campitelli, Jane Kristin Nøstbakken, … Haakon Sjursen *Vaccine* (2011-10) <https://doi.org/dq7db6> DOI: [10.1016/j.vaccine.2011.08.042](https://doi.org/10.1016/j.vaccine.2011.08.042) · PMID: [21864624](https://www.ncbi.nlm.nih.gov/pubmed/21864624)

202. **A 2-Part, Phase 1/2, Randomized, Observer-Blinded Study To Evaluate The Safety And Immunogenicity Of A SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-2 rS) With Or Without MATRIX-M™ Adjuvant In Healthy Subjects** Novavax *clinicaltrials.gov* (2021-07-23) <https://clinicaltrials.gov/ct2/show/NCT04368988>

203. **Evaluation of a SARS-CoV-2 Vaccine NVX-CoV2373 in Younger and Older Adults** Neil Formica, Raburn Mallory, Gary Albert, Michelle Robinson, Joyce S Plested, Iksung Cho, Andreana Robertson, Filip Dubovsky, Gregory M Glenn, for the 2019nCoV-101 Study Group *Cold Spring Harbor Laboratory* (2021-03-01) <https://doi.org/gjh94p> DOI: [10.1101/2021.02.26.21252482](https://doi.org/10.1101/2021.02.26.21252482)

204. **Progress and Prospects on Vaccine Development against SARS-CoV-2** Jinyong Zhang, Hao Zeng, Jiang Gu, Haibo Li, Lixin Zheng, Quanming Zou *Vaccines* (2020-03-29) <https://doi.org/ggq726> DOI: [10.3390/vaccines8020153](https://doi.org/10.3390/vaccines8020153) · PMID: [32235387](https://www.ncbi.nlm.nih.gov/pubmed/32235387) · PMCID: [PMC7349596](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7349596)

205. **Towards an understanding of the adjuvant action of aluminium** Philippa Marrack, Amy S McKee, Michael W Munks *Nature Reviews Immunology* (2009-04) <https://doi.org/drcwvf> DOI: [10.1038/nri2510](https://doi.org/10.1038/nri2510) · PMID: [19247370](https://www.ncbi.nlm.nih.gov/pubmed/19247370) · PMCID: [PMC3147301](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3147301)

206. **DAMP-Inducing Adjuvant and PAMP Adjuvants Parallelly Enhance Protective Type-2 and Type-1 Immune Responses to Influenza Split Vaccination** Tomoya Hayashi, Masatoshi Momota, Etsushi Kuroda, Takato Kusakabe, Shingo Kobari, Kotaro Makisaka, Yoshitaka Ohno, Yusuke Suzuki, Fumika Nakagawa, Michelle SJ Lee, … Hidetoshi Arima *Frontiers in Immunology* (2018-11-20) <https://doi.org/gfqq89> DOI: [10.3389/fimmu.2018.02619](https://doi.org/10.3389/fimmu.2018.02619) · PMID: [30515151](https://www.ncbi.nlm.nih.gov/pubmed/30515151) · PMCID: [PMC6255964](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6255964)

207. **Better Adjuvants for Better Vaccines: Progress in Adjuvant Delivery Systems, Modifications, and Adjuvant–Antigen Codelivery** Zhi-Biao Wang, Jing Xu *Vaccines* (2020-03-13) <https://doi.org/gg35vj> DOI: [10.3390/vaccines8010128](https://doi.org/10.3390/vaccines8010128) · PMID: [32183209](https://www.ncbi.nlm.nih.gov/pubmed/32183209) · PMCID: [PMC7157724](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7157724)

208. **Defining trained immunity and its role in health and disease** Mihai G Netea, Jorge Domínguez-Andrés, Luis B Barreiro, Triantafyllos Chavakis, Maziar Divangahi, Elaine Fuchs, Leo AB Joosten, Jos WM van der Meer, Musa M Mhlanga, Willem JM Mulder, … Eicke Latz *Nature Reviews Immunology* (2020-03-04) <https://doi.org/gg28pr> DOI: [10.1038/s41577-020-0285-6](https://doi.org/10.1038/s41577-020-0285-6) · PMID: [32132681](https://www.ncbi.nlm.nih.gov/pubmed/32132681) · PMCID: [PMC7186935](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7186935)

209. **Trained Immunity: a Tool for Reducing Susceptibility to and the Severity of SARS-CoV-2 Infection** Mihai G Netea, Evangelos J Giamarellos-Bourboulis, Jorge Domínguez-Andrés, Nigel Curtis, Reinout van Crevel, Frank L van de Veerdonk, Marc Bonten *Cell* (2020-05) <https://doi.org/gg2584> DOI: [10.1016/j.cell.2020.04.042](https://doi.org/10.1016/j.cell.2020.04.042) · PMID: [32437659](https://www.ncbi.nlm.nih.gov/pubmed/32437659) · PMCID: [PMC7196902](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7196902)

210. **Reducing Health Care Workers Absenteeism in Covid-19 Pandemic Through BCG Vaccine - Full Text View - ClinicalTrials.gov** <https://clinicaltrials.gov/ct2/show/NCT04328441>

211. **Application of BCG Vaccine for Immune-prophylaxis Among Egyptian Healthcare Workers During the Pandemic of COVID-19** Adel Khattab *clinicaltrials.gov* (2020-04-17) <https://clinicaltrials.gov/ct2/show/NCT04350931>

212. **Performance Evaluation of BCG Vaccination in Healthcare Personnel to Reduce the Severity of SARS-COV-2 Infection in Medellín, Colombia, 2020** Universidad de Antioquia *clinicaltrials.gov* (2020-11-24) <https://clinicaltrials.gov/ct2/show/NCT04362124>

213. **COVID-19: BCG As Therapeutic Vaccine, Transmission Limitation, and Immunoglobulin Enhancement - Full Text View - ClinicalTrials.gov** <https://clinicaltrials.gov/ct2/show/NCT04369794>

214. **Using BCG Vaccine to Protect Health Care Workers in the COVID-19 Pandemic - Full Text View - ClinicalTrials.gov** <https://clinicaltrials.gov/ct2/show/NCT04373291>

215. **Reducing Morbidity and Mortality in Health Care Workers Exposed to SARS-CoV-2 by Enhancing Non-specific Immune Responses Through Bacillus Calmette-Guérin Vaccination, a Randomized Controlled Trial** TASK Applied Science *clinicaltrials.gov* (2020-05-06) <https://clinicaltrials.gov/ct2/show/NCT04379336>

216. **Randomized Controlled Trial Evaluating the Efficacy of Vaccination With Bacillus Calmette and Guérin (BCG) in the Prevention of COVID-19 Via the Strengthening of Innate Immunity in Health Care Workers** Assistance Publique - Hôpitaux de Paris *clinicaltrials.gov* (2020-08-17) <https://clinicaltrials.gov/ct2/show/NCT04384549>

217. **Study to Assess VPM1002 in Reducing Healthcare Professionals' Absenteeism in COVID-19 Pandemic - Full Text View - ClinicalTrials.gov** <https://clinicaltrials.gov/ct2/show/NCT04387409>

218. **A Randomized Clinical Trial for Enhanced Trained Immune Responses Through Bacillus Calmette-Guérin Vaccination to Prevent Infections by COVID-19: The ACTIVATE II Trial** Hellenic Institute for the Study of Sepsis *clinicaltrials.gov* (2020-07-10) <https://clinicaltrials.gov/ct2/show/NCT04414267>

219. **Reducing Hospital Admission of Elderly in SARS-CoV-2 Pandemic Via the Induction of Trained Immunity by Bacillus Calmette-Guérin Vaccination, a Randomized Controlled Trial** Radboud University *clinicaltrials.gov* (2020-06-03) <https://clinicaltrials.gov/ct2/show/NCT04417335>

220. **Study to Assess VPM1002 in Reducing Hospital Admissions and/or Severe Respiratory Infectious Diseases in Elderly in COVID-19 Pandemic - Full Text View - ClinicalTrials.gov** <https://clinicaltrials.gov/ct2/show/NCT04435379>

221. **Efficacy and Safety of VPM1002 in Reducing SARS-CoV-2 (COVID-19) Infection Rate and Severity - Full Text View - ClinicalTrials.gov** <https://clinicaltrials.gov/ct2/show/NCT04439045>

222. **Complex Immune Dysregulation in COVID-19 Patients with Severe Respiratory Failure** Evangelos J Giamarellos-Bourboulis, Mihai G Netea, Nikoletta Rovina, Karolina Akinosoglou, Anastasia Antoniadou, Nikolaos Antonakos, Georgia Damoraki, Theologia Gkavogianni, Maria-Evangelia Adami, Paraskevi Katsaounou, … Antonia Koutsoukou *Cell Host & Microbe* (2020-06) <https://doi.org/ggthxs> DOI: [10.1016/j.chom.2020.04.009](https://doi.org/10.1016/j.chom.2020.04.009) · PMID: [32320677](https://www.ncbi.nlm.nih.gov/pubmed/32320677) · PMCID: [PMC7172841](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7172841)

223. **The Innate Immune System: Fighting on the Front Lines or Fanning the Flames of COVID-19?** Julia L McKechnie, Catherine A Blish *Cell Host & Microbe* (2020-06) <https://doi.org/gg28pq> DOI: [10.1016/j.chom.2020.05.009](https://doi.org/10.1016/j.chom.2020.05.009) · PMID: [32464098](https://www.ncbi.nlm.nih.gov/pubmed/32464098) · PMCID: [PMC7237895](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7237895)

224. **Type I and Type III Interferons – Induction, Signaling, Evasion, and Application to Combat COVID-19** Annsea Park, Akiko Iwasaki *Cell Host & Microbe* (2020-06) <https://doi.org/gg2ccp> DOI: [10.1016/j.chom.2020.05.008](https://doi.org/10.1016/j.chom.2020.05.008) · PMID: [32464097](https://www.ncbi.nlm.nih.gov/pubmed/32464097) · PMCID: [PMC7255347](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7255347)

225. **Viral Mutation Rates** Rafael Sanjuán, Miguel R Nebot, Nicola Chirico, Louis M Mansky, Robert Belshaw *Journal of Virology* (2010-10) <https://doi.org/bc7c55> DOI: [10.1128/jvi.00694-10](https://doi.org/10.1128/jvi.00694-10) · PMID: [20660197](https://www.ncbi.nlm.nih.gov/pubmed/20660197) · PMCID: [PMC2937809](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2937809)

226. **SARS-CoV-2 and influenza: a comparative overview and treatment implications** Laura D Manzanares-Meza, Oscar Medina-Contreras *Boletín Médico del Hospital Infantil de México* (2020-10-23) <https://doi.org/gjj2n7> DOI: [10.24875/bmhim.20000183](https://doi.org/10.24875/bmhim.20000183) · PMID: [33064680](https://www.ncbi.nlm.nih.gov/pubmed/33064680)

227. **Influenza evolution and H3N2 vaccine effectiveness, with application to the 2014/2015 season** Xi Li, Michael W Deem *Protein Engineering Design and Selection* (2016-08) <https://doi.org/f856v5> DOI: [10.1093/protein/gzw017](https://doi.org/10.1093/protein/gzw017) · PMID: [27313229](https://www.ncbi.nlm.nih.gov/pubmed/27313229) · PMCID: [PMC4955871](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4955871)

228. **Neutralizing Activity of BNT162b2-Elicited Serum** Yang Liu, Jianying Liu, Hongjie Xia, Xianwen Zhang, Camila R Fontes-Garfias, Kena A Swanson, Hui Cai, Ritu Sarkar, Wei Chen, Mark Cutler, … Pei-Yong Shi *New England Journal of Medicine* (2021-04-15) <https://doi.org/fwsc> DOI: [10.1056/nejmc2102017](https://doi.org/10.1056/nejmc2102017) · PMID: [33684280](https://www.ncbi.nlm.nih.gov/pubmed/33684280) · PMCID: [PMC7944950](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7944950)

229. **Covid-19 vaccine effectiveness affected by variants** <https://www.pharmaceutical-technology.com/comment/covid-19-vaccine-effectiveness-affected-by-variants/>

230. **The effects of virus variants on COVID-19 vaccines** <https://www.who.int/news-room/feature-stories/detail/the-effects-of-virus-variants-on-covid-19-vaccines>

231. **Predicting Influenza H3N2 Vaccine Efficacy From Evolution of the Dominant Epitope** Melia E Bonomo, Michael W Deem *Clinical Infectious Diseases* (2018-10-01) <https://doi.org/gf33js> DOI: [10.1093/cid/ciy323](https://doi.org/10.1093/cid/ciy323) · PMID: [29672670](https://www.ncbi.nlm.nih.gov/pubmed/29672670)

232. **Looking beyond COVID-19 vaccine phase 3 trials** Jerome H Kim, Florian Marks, John D Clemens *Nature Medicine* (2021-01-19) <https://doi.org/ght28p> DOI: [10.1038/s41591-021-01230-y](https://doi.org/10.1038/s41591-021-01230-y) · PMID: [33469205](https://www.ncbi.nlm.nih.gov/pubmed/33469205)

233. **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)

234. **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* (2020-09-11) <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)

235. **Vaccine optimization for COVID-19: Who to vaccinate first?** Laura Matrajt, Julia Eaton, Tiffany Leung, Elizabeth R Brown *Science Advances* (2021-02-03) <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)

236. **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)

237. **Strategic spatiotemporal vaccine distribution increases the survival rate in an infectious disease like Covid-19** Jens Grauer, Hartmut Löwen, Benno Liebchen *Scientific Reports* (2020-12-09) <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)

238. **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)

239. **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)

240. **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)

241. **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>

242. **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>

243. **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>

244. **Vaccine development and approval in Canada** Health Canada (2020-12-08) <https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/drugs-vaccines-treatments/vaccines/development-approval-infographic.html>

245. **Vaccines and treatments for COVID-19: Safety after authorization** Public Health Agency of Canada (2020-12-03) <https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/prevention-risks/covid-19-vaccine-treatment/safety-after-authorization.html>

246. **Drug and vaccine authorizations for COVID-19: List of applications received** Health Canada (2020-09-17) <https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/drugs-vaccines-treatments/authorization/applications.html>

247. **An earlier end date for vaccination campaign is 'possible', Trudeau says | CBC News** John Paul Tasker ·CBC News · *CBC* <https://www.cbc.ca/news/politics/trudeau-possible-vaccination-campaign-ends-sooner-1.5934994>

248. **The Advisory Committee on Immunization Practices’ Interim Recommendation for Allocating Initial Supplies of COVID-19 Vaccine — United States, 2020** Kathleen Dooling, Nancy McClung, Mary Chamberland, Mona Marin, Megan Wallace, Beth P Bell, Grace M Lee, HKeipp Talbot, José R Romero, Sara E Oliver *MMWR. Morbidity and Mortality Weekly Report* (2020-12-11) <https://doi.org/gjkxrm> DOI: [10.15585/mmwr.mm6949e1](https://doi.org/10.15585/mmwr.mm6949e1) · PMID: [33301429](https://www.ncbi.nlm.nih.gov/pubmed/33301429) · PMCID: [PMC7737687](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7737687)

249. **The Advisory Committee on Immunization Practices’ Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine — United States, December 2020** Sara E Oliver, Julia W Gargano, Mona Marin, Megan Wallace, Kathryn G Curran, Mary Chamberland, Nancy McClung, Doug Campos-Outcalt, Rebecca L Morgan, Sarah Mbaeyi, … Kathleen Dooling *MMWR. Morbidity and Mortality Weekly Report* (2020-12-18) <https://doi.org/ghvnsf> DOI: [10.15585/mmwr.mm6950e2](https://doi.org/10.15585/mmwr.mm6950e2) · PMID: [33332292](https://www.ncbi.nlm.nih.gov/pubmed/33332292) · PMCID: [PMC7745957](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7745957)

250. **US administers 1st doses of Pfizer coronavirus vaccine** ABC News *ABC News* <https://abcnews.go.com/US/us-administer-1st-doses-pfizer-coronavirus-vaccine/story?id=74703018>

251. **The Advisory Committee on Immunization Practices’ Interim Recommendation for Use of Moderna COVID-19 Vaccine — United States, December 2020** Sara E Oliver, Julia W Gargano, Mona Marin, Megan Wallace, Kathryn G Curran, Mary Chamberland, Nancy McClung, Doug Campos-Outcalt, Rebecca L Morgan, Sarah Mbaeyi, … Kathleen Dooling *MMWR. Morbidity and Mortality Weekly Report* (2021-01-01) <https://doi.org/gh77ch> DOI: [10.15585/mmwr.mm695152e1](https://doi.org/10.15585/mmwr.mm695152e1) · PMID: [33382675](https://www.ncbi.nlm.nih.gov/pubmed/33382675)

252. **The Advisory Committee on Immunization Practices’ Updated Interim Recommendation for Allocation of COVID-19 Vaccine — United States, December 2020** Kathleen Dooling, Mona Marin, Megan Wallace, Nancy McClung, Mary Chamberland, Grace M Lee, HKeipp Talbot, José R Romero, Beth P Bell, Sara E Oliver *MMWR. Morbidity and Mortality Weekly Report* (2021-01-01) <https://doi.org/ghqfvr> DOI: [10.15585/mmwr.mm695152e2](https://doi.org/10.15585/mmwr.mm695152e2) · PMID: [33382671](https://www.ncbi.nlm.nih.gov/pubmed/33382671)

253. **The Moderna vaccine is now in some Americans' arms as Covid-19 cases in the US pass 18 million** Madeline Holcombe CNN Holly Yan and Steve Almasy *CNN* <https://www.cnn.com/2020/12/21/health/us-coronavirus-monday/index.html>

254. **Janssen COVID-19 Vaccine** Office of the Commissioner *FDA* (2021-09-15) <https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/janssen-covid-19-vaccine>

255. **The Advisory Committee on Immunization Practices’ Interim Recommendation for Use of Janssen COVID-19 Vaccine — United States, February 2021** Sara E Oliver, Julia W Gargano, Heather Scobie, Megan Wallace, Stephen C Hadler, Jessica Leung, Amy E Blain, Nancy McClung, Doug Campos-Outcalt, Rebecca L Morgan, … Kathleen Dooling *MMWR. Morbidity and Mortality Weekly Report* (2021-03-05) <https://doi.org/gh77cj> DOI: [10.15585/mmwr.mm7009e4](https://doi.org/10.15585/mmwr.mm7009e4) · PMID: [33661860](https://www.ncbi.nlm.nih.gov/pubmed/33661860) · PMCID: [PMC7948932](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7948932)

256. **WHO adds Janssen vaccine to list of safe and effective emergency tools against COVID-19** <https://www.who.int/news/item/12-03-2021-who-adds-janssen-vaccine-to-list-of-safe-and-effective-emergency-tools-against-covid-19>

257. **COVID-19 Vaccine Distribution: The Process** Assistant Secretary for Public Affairs (ASPA) *HHS.gov* (2020-12-16) <https://www.hhs.gov/coronavirus/covid-19-vaccines/distribution/index.html>

258. **COVID Data Tracker** CDC *Centers for Disease Control and Prevention* (2020-03-28) <https://covid.cdc.gov/covid-data-tracker>

259. **Biden now says US will have enough vaccine for every adult by the end of May** Kevin Liptak CNN Jeff Zeleny and John Harwood *CNN* <https://www.cnn.com/2021/03/02/politics/biden-merck-johnson--johnson-vaccine/index.html>

260. **Covid-19: Was US vaccine rollout a 'dismal failure' under Trump?** BBC News (2021-01-26) <https://www.bbc.com/news/world-us-canada-55721437>

261. **Structured to Fail: Lessons from the Trump Administration's Faulty Pandemic Planning and Response** Alejandro E Camacho, Robert L Glicksman *Social Science Research Network* (2021-01-21) <https://papers.ssrn.com/abstract=3770368>

262. **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)

263. **South Africa starts administering Janssen COVID-19 vaccine to health workers** Rachel Arthur *BioPharma-Reporter* (2021-02-18) <https://www.biopharma-reporter.com/Article/2021/02/18/South-Africa-starts-administering-Janssen-COVID-19-vaccine-to-health-workers>

264. **EMA receives application for conditional marketing authorisation of COVID-19 Vaccine Janssen** Ana Catarina PINHO *European Medicines Agency* (2021-02-16) <https://www.ema.europa.eu/en/news/ema-receives-application-conditional-marketing-authorisation-covid-19-vaccine-janssen>

265. **Merck will help make Johnson & Johnson coronavirus vaccine as rivals team up to help Biden accelerate shots** Washington Post <https://www.washingtonpost.com/health/2021/03/02/merck-johnson-and-johnson-covid-vaccine-partnership/>

266. **The UK has approved a COVID vaccine — here’s what scientists now want to know** Heidi Ledford, David Cyranoski, Richard Van Noorden *Nature* (2020-12-03) <https://doi.org/gh4xmm> DOI: [10.1038/d41586-020-03441-8](https://doi.org/10.1038/d41586-020-03441-8) · PMID: [33288887](https://www.ncbi.nlm.nih.gov/pubmed/33288887)

267. **EMA recommends first COVID-19 vaccine for authorisation in the EU** Ana Catarina PINHO *European Medicines Agency* (2020-12-21) <https://www.ema.europa.eu/en/news/ema-recommends-first-covid-19-vaccine-authorisation-eu>

268. **Regulatory approval of Vaxzevria (previously COVID-19 Vaccine AstraZeneca)** GOV.UK <https://www.gov.uk/government/publications/regulatory-approval-of-covid-19-vaccine-astrazeneca>

269. **EMA recommends COVID-19 Vaccine AstraZeneca for authorisation in the EU** Ana Catarina PINHO *European Medicines Agency* (2021-01-29) <https://www.ema.europa.eu/en/news/ema-recommends-covid-19-vaccine-astrazeneca-authorisation-eu>

270. **Covid: Brian Pinker, 82, first to get Oxford-AstraZeneca vaccine** BBC News (2021-01-04) <https://www.bbc.com/news/uk-55525542>

271. **Spikevax (previously COVID-19 Vaccine Moderna)** Dagmara CZARSKA-THORLEY *European Medicines Agency* (2021-01-04) <https://www.ema.europa.eu/en/medicines/human/EPAR/spikevax>

272. **Regulatory approval of Spikevax (formerly COVID-19 Vaccine Moderna)** GOV.UK <https://www.gov.uk/government/publications/regulatory-approval-of-covid-19-vaccine-moderna>

273. **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>

274. **Bloomberg - Are you a robot?** <https://www.bloomberg.com/tosv2.html?vid=&uuid=9cfac136-1a1d-11ec-a635-426b7a74654e&url=L25ld3MvYXJ0aWNsZXMvMjAyMC0xMi0wMi93aXRoaW4taG91cnMtb2YtdS1rLXB1dGluLW9yZGVycy1zdGFydC1vZi1tYXNzLWNvdmlkLTE5LXNob3Rz>

275. **Facing Record Covid-19 Case Rise, Russia Rolls Out Sputnik V Vaccine** James Rodgers *Forbes* <https://www.forbes.com/sites/jamesrodgerseurope/2020/12/05/facing-record-covid-19-case-rise-russia-rolls-out-sputnik-v-vaccine/>

276. **Clarification on Sputnik V vaccine in the EU approval process** Ana Catarina PINHO *European Medicines Agency* (2021-02-10) <https://www.ema.europa.eu/en/news/clarification-sputnik-v-vaccine-eu-approval-process>

277. **Countries are lining up for Russia's once-scorned Sputnik vaccine after strong efficacy results** Fortune <https://fortune.com/2021/02/08/international-sputnik-russia-demand/>

278. **Russian Direct Investment Fund** <https://rdif.ru/Eng_fullNews/5858/>

279. **Unable to get U.S. vaccines, world turns to Russia and China** Ryan Heath *POLITICO* <https://www.politico.com/news/2021/02/25/global-vaccine-public-relations-war-471665>

280. **Germany moves to bring Russian vaccine into EU orbit** France 24 (2021-02-03) <https://www.france24.com/en/live-news/20210203-germany-moves-to-bring-russian-vaccine-into-eu-orbit>

281. **Russia approves its third COVID-19 vaccine, CoviVac** Reuters (2021-02-20) <https://www.reuters.com/article/us-health-coronavirus-russia-vaccine-idUSKBN2AK07H>

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

283. **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>

284. **Covid-19 Africa: What is happening with vaccine supplies?** BBC News (2021-09-10) <https://www.bbc.com/news/56100076>

285. **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)

286. **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>

287. **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)

288. **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)

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

290. **Countries now scrambling for COVID-19 vaccines may soon have surpluses to donate** Jon Cohen *Science* (2021-03-09) <https://doi.org/gh77cf> DOI: [10.1126/science.abh4476](https://doi.org/10.1126/science.abh4476)

291. **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>

292. **Pfizer and BioNTech to Submit Emergency Use Authorization Request Today to the U.S. FDA for COVID-19 Vaccine | Pfizer** <https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-submit-emergency-use-authorization>

293. **Moderna Announces First Participants Dosed in Phase 2/3 Study of COVID-19 Vaccine Candidate in Adolescents | Moderna, Inc.** <https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-first-participants-dosed-phase-23-study-covid/>