Vaccine Development Strategies for SARS-CoV-2

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## 0.1 Abstract

In the 21st century, several emergent viruses have emphasized the particular value of rapid and scalable vaccine development programs. During the current pandemic caused by *Severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2), recent biotechnological advances in vaccine design have facilitated the development and deployment of vaccines at an unprecedented pace. The genome sequence of SARS-CoV-2 was released in January 2020, allowing for global efforts in vaccine development to begin within two weeks of the international community becoming aware of the new viral threat. Technologies that were previously only theoretical have been used to develop SARS-CoV-2 vaccines that have now been deployed worldwide. Although historically a slow process, vaccine development in the face of COVID-19 reveals a major shift in vaccine technologies. In this review, we contextualize COVID-19 vaccine development in the broader vaccine landscape. We describe where these candidates currently stand in terms of efficacy, safety, and approval and discuss patterns in worldwide distribution. The SARS-CoV-2 pandemic provides an exceptional illustration of how rapidly vaccine development technology has advanced in the last two decades in particular.

## 0.2 Importance

The SARS-CoV-2 pandemic has caused untold damage globally, presenting unusual opportunities and demands in vaccine development. As of May 6, 2022, SARS-CoV-2 has infected over 516,758,993 and taken the lives of 6,249,626 people globally. The development, production, and distribution of vaccines is imperative to saving lives, preventing illness, and reducing the economic and social burdens caused by the COVID-19 pandemic. Effective deployment is critical to reducing the susceptibility of worldwide populations, especially in light of emerging variants. 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

Vaccine development has historically been slow. The past 20 years have seen several previously unknown viruses emerge and rise rapidly to pose a global threat, challenging vaccine developers to explore approaches that would facilitate a rapid response to novel viruses. Unsurprisingly, in the current century, significant advances have been made in vaccine development based on advances in genomics.

Vaccine technologies that require only minor adjustments for novel viral threats are appealing because this modular approach would mean they could enter trials quickly in response to a new pathogen of concern. Traditional vaccine technologies were built on the principle of using either a weakened version of the virus or a fragment of the virus, while recent years have seen a paradigm shift towards reverse vaccinology. Reverse vaccinology emphasizes a hypothesis-free approach to vaccine development [[1](#ref-jU9YFYvB)]. This strategy was explored during development of a DNA vaccine against the Zika virus [[2](#ref-u0dESADU)]. While once again the disease was controlled before the vaccine became available [[3](#ref-HyYY2agc)], the response demonstrated the potential for modular technologies to facilitate a response to emerging viral threats [[2](#ref-u0dESADU)]. The potential for such vaccines to benefit the field of oncology has encouraged vaccine developers to invest in next-generation approaches, which has spurred the diversification of vaccine development programs [[4](#ref-wPl93ATP),[5](#ref-BsrTDzJ2)]. As a result, during the COVID-19 pandemic, these modular technologies have taken center stage in controlling a viral threat for the first time.

Emergent viral threats of the 21st century include severe acute respiratory syndrome (SARS), “swine flu” (H1N1), Middle East respiratory syndrome (MERS), Ebola virus disease (EVD), and now COVID-19, all of which have underscored the importance of a rapid global response to a new infectious virus. Because vaccines fail to provide immediate prophylactic protection or treatment of ongoing infections, their application to most of these epidemics has been limited [[6](#ref-181QWa7HL)]. One of the more successful recent vaccine development programs was for H1N1 influenza. This program benefited from the strong existing infrastructure for influenza vaccines along with the fact that regulatory agencies had determined that vaccines produced using egg- and cell-based platforms could be licensed under the regulations used for a strain change [[3](#ref-HyYY2agc)]. Although a monovalent H1N1 vaccine was not available before the pandemic peaked in the United States and Europe, it became available soon afterward as a stand-alone vaccine that was eventually incorporated into commercially available seasonal influenza vaccines [[3](#ref-HyYY2agc)]. Critiques of the production and distribution of the H1N1 vaccine have stressed the need for alternative development-and-manufacturing platforms that can be readily adapted to new pathogens.

The pandemic caused by SARS-CoV-2 has highlighted a confluence of circumstances that positioned vaccine development as a key player in efforts to control the virus and mitigate its damage. This virus did not follow the same trajectory as other emergent viruses of recent note, such as SARS-CoV-1, MERS-CoV, and Ebola virus, none of which reached the level of pandemic. Spread of the SARS-CoV-2 virus has remained out of control in many parts of the world into 2022, especially with the emergence of novel variants exhibiting increased rates of transmission [[7](#ref-GdZc4Yyd)]. While, for a variety of reasons, SARS-CoV-2 was not controlled as rapidly as the viruses underlying prior 21st century epidemics [[8](#ref-njpLhBui)], vaccine development technology had also progressed based on these and other prior viral threats to the point that a rapid international vaccine development response was possible.

Vaccines bolster the immune response to the virus at the population level, thereby driving a lower rate of infection and likely significantly reducing fatalities even for a highly infectious virus like SARS-CoV-2. The first critical step towards developing a vaccine against SARS-CoV-2 was characterizing the viral target, which happened extremely early in the COVID-19 outbreak with the sequencing and dissemination of the viral genome in early January 2020 [[9](#ref-vlGP3RAU)] (Figure [1](#fig:virus)). This genomic information allowed for an early identification of the sequence of the spike (S) protein (Figure [1](#fig:virus)), which is the antigen and induces an immune response [[10](#ref-Vnbw9o3T),[11](#ref-13wCBLnnu)].

The Coalition for Epidemic Preparedness Innovations (CEPI) is coordinating global health agencies and pharmaceutical companies to develop vaccines against SARS-CoV-2. As early as September 2020, there were over 180 vaccine candidates against SARS-CoV-2 in development [[12](#ref-dqpEe5Lz)]. While little is currently known about immunity to SARS-CoV-2, vaccine developers typically tests for serum neutralizing activity, as this has been established as a biomarker for adaptive immunity in other respiratory illnesses [[13](#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 3 trials where the effect of the vaccine on a cohort’s likelihood of contracting SARS-CoV-2 is evaluated. With vaccine candidates at all stages of development, including full approval of some vaccines, the vaccine development landscape for COVID-19 includes vaccines produced by a wide array of technologies. Examining the vaccine development programs tackling the COVID-19 pandemic alongside other 21st century efforts to control emerging viral threats demonstrates the significant biotechnological advances in this field and the importance of modular and adaptable approaches to vaccination. Here, we review the various technologies being explored for the development of SARS-CoV-2 vaccines globally.



Figure 1: **Structure of the SARS-CoV-2 virus.** The development of vaccines depends on the immune system recognizing the virus. Here, the structure of SARS-CoV-2 is represented both in the abstract and against a visualization of the virion. The abstracted visualization was made using BioRender [[14](#ref-14FBejgLM)] and the microscopy was conducted by the National Institute of Allergy and Infectious Diseases [[15](#ref-Jzj97hJh)].

## 0.4 Cross-Platform Considerations in Vaccine Development

Certain design decisions are relevant to vaccine development across multiple platforms. One applies to platforms that deliver the antigen, which in the case of SARS-CoV-2 vaccines is the Spike (S) protein. The prefusion conformation of the SARS-CoV-2 S protein, which is the structure before the virus fuses to the host cell membrane, is metastable [[16](#ref-R7Xdh5nH)], and the release of energy during membrane fusion drives this process forward following destabilization [[17](#ref-17DSmRo9H),[18](#ref-3uddYea8)]. Due to the significant conformational changes that occur during membrane fusion [[19](#ref-qcVbT0w4),[20](#ref-hIc3bKWe),[21](#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 [[22](#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 [[22](#ref-oghHqZDt),[23](#ref-13wWdgODZ),[24](#ref-OVsxrEuX)] (see also [[7](#ref-GdZc4Yyd)]). Vaccine developers can stabilize the prefusion conformer by selecting versions of the S protein containing mutations that lock the position [[25](#ref-lvq9hGmj)]. The immune response to the spike protein when it is stabilized in this conformation is improved over other S structures [[26](#ref-10UC562ga)]. Thus, vaccines that use this prefusion stabilized conformation are expected to not only offer improved immunogenicity, but also be more resilient to the accumulation of mutations in SARS-CoV-2.

Another cross-platform consideration is the use of adjuvants. Adjuvants include a variety of molecules or larger microbial-related products that affect the immune system broadly or an immune response of interest. They can either be comprised of or contain immunostimulants or immunomodulators. Adjuvants are sometimes included within vaccines in order to enhance the immune response. Different adjuvants can regulate different types of immune responses, so the type or combination of adjuvants used in a vaccine will depend on both the type of vaccine and concern related to efficacy and safety. A variety of possible mechanisms for adjuvants have been investigated [[27](#ref-13bVbfc5h),[28](#ref-122h6fIxE),[29](#ref-uO0uqhxc)].

Due to viral evolution, vaccine developers are in an arms race with a pathogen that benefits from mutations that reduce its susceptibility to adaptive immunity. The evolution of several variants of concern (VOC) presents significant challenges for vaccines developed based on the index strain identified in Wuhan in late 2019. We discuss these variants in depth elsewhere [[30](#ref-17qiILENK)]. To date, the most significant variants of concern identified are alpha (2020), beta (2020), gamma (2020), delta (2021) and omicron (2021). The efficacy of vaccines in the context of these variants is discussed where information is available.

Finally,

## 0.5 COVID-19 Vaccine Development Platforms



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

The first administration of a dose of a COVID-19 vaccine to a human trial participant occurred on March 16, 2020 [[31](#ref-fQvzeptv),[32](#ref-1GA95MF2m)], marking an extremely rapid response to the emergence of SARS-CoV-2. Within a few weeks, at least 78 vaccine development programs were active [[32](#ref-1GA95MF2m)]. These programs employ a variety of technologies (Figure [2](#fig:vaccines)), ranging from established approaches to novel technologies that had never previously gone to market. As of May 17, 2022, 38 SARS-CoV-2 vaccines have been approved world wide and 27 are being administered throughout the world, with 12 billion doses administered across countries. Many vaccines are available in only a subset of countries, and the types of vaccines available varies widely throughout the world. The status of individual vaccines continues to change and varies regionally.

While traditional methods of vaccine development such as inactivated whole viruses are still used today (Figure [2](#fig:vaccines)), biomedical research in the 21st century has been significantly influenced by the genomic revolution, and vaccine development is no exception. The shift towards omics-based approaches to vaccine development began to take hold with the development of the meningococcal type B vaccine using reverse vaccinology in the early 2010s [[33](#ref-MCZBJ5sF),[34](#ref-fw8IwtHq)]. In this way, the genomic revolution catalyzed a fundamental shift in the development of vaccines. These vaccine technologies could potentially provide a future approach to addressing one of the major limitations of vaccines today due to their potential to function therapeutically rather than just prophylactically [[35](#ref-kqerKJKY)].

Nucleic-acid based approaches are all based on the shared underlying principle that utilizing a vector to deliver the information to produce an antigen can trigger an immune response to the antigen without introducing an infectious agent. Such approaches build on subunit vaccination strategies, where a component of a vaccine (e.g., an antigenic protein) is delivered. Platforms based on genomic sequencing began to be explored beginning in the 1980s as genetic research became increasingly feasible. Advances in genetic engineering allowed for gene sequences of specific viral antigens to be grown *in vitro* [[36](#ref-YY3x3bBV)]. Studies also demonstrated that model organisms could be induced to construct antigens that would trigger an immune response [[37](#ref-U9ZIZWkB),[38](#ref-pWMIo6pD),[39](#ref-uPszIvSj)]. These two developments meant that it could be possible to identify any or all of the antigens encoded by a virus’s genome and train the immune response to recognize them.

In nucleic-acid-based approaches, the genome of a pathogen is screened to identify potential vaccine targets [[34](#ref-fw8IwtHq)], and pathogens of interest are then expressed *in vitro* and tested in animal models to determine their immunogenicity [[34](#ref-fw8IwtHq)]. By inducing the host to express the antigen, such vaccines can activate immune pathways via both MHC I and MHC II [[40](#ref-fwumPoq1)] instead of MHC II alone as with prior technologies [[39](#ref-uPszIvSj)], meaning that both humoral and cellular immunity are activated [[5](#ref-BsrTDzJ2)]. Thus, in addition to lacking an infectious agent, these approaches are likely to offer several advantages over more traditional immunization platforms because they can stimulate both B- and T-cell responses [[5](#ref-BsrTDzJ2),[41](#ref-29LxSWHB)].

The delivery and presentation of antigens is fundamental to inducing immunity against a virus. Vaccines that deliver nucleic acids allow the introduction of foreign substances to the body to induce both humoral and cellular immune responses [[5](#ref-BsrTDzJ2)]. Delivering a nucleic acid sequence to host cells allows the host to synthesize an antigen without exposure to a viral threat [[5](#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 [[5](#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 [[5](#ref-BsrTDzJ2)]. Here, opportunities can 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.

#### 0.5.0.1 DNA Vaccines

Nucleic acid information can be deliver antigen information to host cells using DNA. However, early attempts to use these technologies to develop vaccines revealed that DNA translated poorly to humans due to low immunogenicity [[37](#ref-U9ZIZWkB),[39](#ref-uPszIvSj),[42](#ref-12jFcMeQY)]. Initially, concerns were raised that DNA vaccines might bind to the host genome or induce autoimmune disease [[5](#ref-BsrTDzJ2),[40](#ref-fwumPoq1)], but pre-clinical and clinical studies have consistently disproved this hypothesis and indicated DNA vaccines to be safe [[42](#ref-12jFcMeQY)]. Many of the safety concerns raised about DNA vaccines were not found to be an issue during preclinical and phase 1 testing, although antibiotic resistance introduced during the plasmid selection process remained a concern during this initial phase of development [[5](#ref-BsrTDzJ2)]. However, the immunogenicity of these vaccines has also not reached expectations [[5](#ref-BsrTDzJ2)]. Despite initially disappointing immunogenicity in clinical trials [[39](#ref-uPszIvSj)], a number of developments during the 2010s led to greater efficacy of DNA vaccines [[5](#ref-BsrTDzJ2)]. However, no DNA vaccines had been approved for use in humans prior to the COVID-19 pandemic [[42](#ref-12jFcMeQY),[43](#ref-yriARFOF)].

Table 1: Approved DNA vaccines [[44](#ref-jswAyWIs)]

| Vaccine | Company | Platform |
| --- | --- | --- |
| Convidecia | CanSino | non replicating viral vector |
| Gam-COVID-Vac | Gamaleya | non replicating viral vector |
| Sputnik Light | Gamaleya | non replicating viral vector |
| Sputnik V | Gamaleya | non replicating viral vector |
| Ad26.COV2.S | Janssen (Johnson & Johnson) | non replicating viral vector |
| Vaxzevria | Oxford/AstraZeneca | non replicating viral vector |
| Covishield (Oxford/ AstraZeneca formulation) | Serum Institute of India | non replicating viral vector |
| ZyCoV-D | Zydus Cadila | plasmid vectored |

#### 0.5.0.2 Plasmid-Vectored DNA Vaccines

**Mechanism:** Many DNA vaccines use a plasmid vector-based approach, where 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 [[45](#ref-XnrBoKVk)]. Plasmids can also be designed to act as adjuvants by encoding molecules that supplement the immune response, such as immune stimulant molecules [[40](#ref-fwumPoq1)]. The DNA itself may also stimulate the innate immune response [[39](#ref-uPszIvSj),[46](#ref-5fcD0JWR)]. Once the plasmid brings the DNA sequence to an 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 [[5](#ref-BsrTDzJ2)]. The vectors are edited to remove extra sequences [[46](#ref-5fcD0JWR)]. Advances such as this on the manufacturing side have improved the safety and throughput of this platform [[46](#ref-5fcD0JWR)].

**Prior Applications:** In the 1990s and 2000s, DNA vaccines delivered via plasmids sparked significant scientific interest, leading to a large number of preclinical trials [[5](#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 1 testing of the application of this technology to HIV, influenza, malaria, and other diseases of concern during this period [[5](#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 [[5](#ref-BsrTDzJ2)].

Early plasmid-vectored DNA vaccine trials targeted HIV and subsequently diseases of worldwide importance such as malaria and hepatitis B [[47](#ref-3EKs730C)]. The concern with these early development projects was immunogenicity, not safety [[47](#ref-3EKs730C)]. Around the turn of the millennium, a hepatitis B vaccine development program demonstrated that these vaccines can induce both antibody and cellular immune response [[48](#ref-jPpzjaYO)]. As of 2018, however, only two plasmid-vectored DNA vaccines had been approved for commercial use, and both were for veterinary populations [[49](#ref-fgs4epPY)].

**Applications to COVID-19:** Several plasmid-vectored DNA vaccines have been developed against COVID-19 (Table [1](#tbl:approved_DNA)). In fact, the ZyCoV-D vaccines developed by India’s Zydus Cadila is the first plasmid-vectored DNA to receive approval for administration [[50](#ref-AfMvzFuk),[51](#ref-eIn1Qf3N)]. Similarly, another plasmid-vectored DNA vaccine, INO-4800 [[52](#ref-xuzLfS0y)], was developed by Inovio Pharmaceuticals Technology. Instead of the needle-free injection system used for ZyCoV-D, INO-4800 uses electroportion. Electroporation was developed as a solution to the issue of limited immunogenicity by increasing the permeability of cell membranes by delivering electrical pulses [[53](#ref-1Hsm2J1sc)]. It has been shown that electroporation can enhance vaccine efficacy by up to 100-fold, as measured by increases in antigen-specific antibody titers [[54](#ref-H6tWVs5R)]. 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. For INO-4800, a plasmid-vectored vaccine is delivered through intradermal injection which is then followed by electroporation with a device known as CELLECTRA® [[55](#ref-4xraQp8j)]. 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 [[53](#ref-1Hsm2J1sc)]. These two vaccines therefore represent two different implementations of a new platform technology. In particular, they offer the advantage of a temperature-stable vaccine, facilitating worldwide administration [[56](#ref-OYnqjMlC)]. Although an exciting development in DNA vaccines, the cost of vaccine manufacturing and electroporation may make scaling the use of this technology for prophylactic use for the general public difficult.

**Trial Safety and Immunogenicity:** For INO-4800, the phase 1 trial began enrolling participants in April 2020 in Philadelphia, PA at the Perelman School of Medicine and at the Center for Pharmaceutical Research in Kansas City, MO. This trial examined two different doses administered in a two-dose regimen [[55](#ref-4xraQp8j)]. Among the 39 participants, only six AEs were reported and all were grade 1 [[55](#ref-4xraQp8j)]. Efficacy was evaluated based on blood samples collected pre- and post-vaccination, and all but three participants of 38 included in the analysis were found to have serum IgG binding titers to the spike protein after vaccination [[55](#ref-4xraQp8j)]. Results from the phase 2 trial were released as a preprint in May 2021 and reported findings based on administering INO-4800 to 401 adult volunteers at high risk of exposure to SARS-CoV-2 [[56](#ref-OYnqjMlC)]. The phase 2 results supported that the vaccine was safe, with 1,446 treatment-related AEs observed across 281 participants, all but one of which were grade 1 or grade 2. The single grade 3 event was joint stiffness [[56](#ref-OYnqjMlC)]. The rates of AEs in the placebo group are not reported. In terms of immunogenicity, pre- and post-vaccination blood samples were again collected and were evaluated for a humoral immune response to the spike protein, and the treatment group was identified to show significantly greater neutralizing activity than the placebo group [[56](#ref-OYnqjMlC)]. The phase 2/3 trials are ongoing in several countries, including the United States, Mexico, India, and Colombia [[57](#ref-17mJcuaPN)/default.aspx,[58](#ref-R79Wr1hU),[59](#ref-yraL6YQa),[60](#ref-Wk6spoae)]. Therefore, vaccine efficacy data from a large study population is not yet available.

**Real-World Safety and Efficacy:** Because phase 3 data is not yet available for INO-4800, the VE is not yet know. However, studies have examined the ability of INO-4800 to induce an immune response that can neutralize VOC. They assessed neutralization of several VOC relative to the index strain [[61](#ref-mbBuH8XY)]. They found no difference in neutralization between the index strain and the gamma VOC (P.1), but neutralization of the alpha and beta VOC was significantly lower (approximately two and seven times, respectively) [[61](#ref-mbBuH8XY)]. These findings are in line with the shifts in efficacy reported for other vaccines.

In addition to loss of neutralizing activity due to viral evolution, studies have also evaluated the decline in nAbs over time. Levels of nAbs remained statistically significant relative to the pre-vaccination baseline for six months [[62](#ref-CSlbNoGU)]. Administration of a booster dose induced a significant increase of titers relative to their pre-booster levels [[62](#ref-CSlbNoGU)]. Given the timing of this trial (enrollment between 6 April and 7 July 2020), it is unlikely that participants were exposed to VOC associated with decreased efficacy. Therefore, this study cannot speak to the efficacy of this vaccine against these variants.

In light of the emergence of VOC against which many vaccines show lower efficacy, Inovio Pharmaceuticals began to develop a new vaccine with the goal of improving robustness against known and future VOC [[63](#ref-ysgD4Dcf)]. Known as INO-4802, this vaccine was designed to express a pan-Spike immunogen [[64](#ref-Aynz3sBj)]. Booster studies in rodents [[65](#ref-12zreC1Tk)] and non-human primates [[64](#ref-Aynz3sBj)] suggest that it may be more effective than INO-4800 in providing immunity to VOC such as delta and omicron when administered as part of a heterologous boost regimen, although boosting with INO-4800 was also very effective in increasing immunity in rhesus macaques [[64](#ref-Aynz3sBj)]. Therefore, boosting is likely to be an important strategy for this vaccine, especially as the virus continues to evolve.

#### 0.5.0.3 Viral-Vectored DNA Vaccines

**Mechanism:** 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. 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 [[66](#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 [[67](#ref-1FpZkxdl4)]. Once the plasmid or viral vector brings the DNA sequence to an 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 [[5](#ref-BsrTDzJ2)]. These vaccines can be either replicating or non-replicating [[68](#ref-bgKUtUIL)].

One of the early viral vectors explored was adenovirus, with serotype 5 (Ad5) being particularly effective [[5](#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 [[5](#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 [[5](#ref-BsrTDzJ2),[69](#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) [[70](#ref-Jkm7jfS8)].

Today, various viral-vector platforms including poxviruses [[71](#ref-8bpbvIro),[72](#ref-1AZfAQ5py)], adenoviruses [[73](#ref-zX5UKhti)], and vesicular stomatitis viruses [[74](#ref-SNwg8Qkf),[75](#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 [[73](#ref-zX5UKhti),[76](#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 [[77](#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 [[77](#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 [[78](#ref-IUplTKEg)].

**Prior Applications:** There are several viral vector vaccines that are available for veterinary use [[5](#ref-BsrTDzJ2),[79](#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 [[80](#ref-9g5tmszW)]. Additionally, several phase 1 and phase 2 clinical trials for other vaccines are ongoing [[66](#ref-1Ff2BDzkT)], and the technology is currently being explored for its potential against numerous infectious diseases including malaria [[81](#ref-OZJWUaDW),[82](#ref-3tkGuMXx)], ebola [[83](#ref-AgZwwt5u),[84](#ref-9BEMTYn8),[85](#ref-PbGQOOI)], and human immunodeficiency virus (HIV) [[86](#ref-1C8hgfvDF),[87](#ref-SAIfGNkZ)]. The threat of MERS and SARS initiated interest in the application of viral vector vaccines to human coronaviruses [[70](#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 [[88](#ref-umEOWDY5)], but were later found to offer incomplete protection in ferret models [[89](#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 [[90](#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 [[91](#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 [[92](#ref-3NtMBDMM)]. The second reported promising results from a phase 1 trial that administered the vaccine to adults and measured safety/tolerability and immune response (as indicated through immune assays following vaccination) [[93](#ref-ERfSJf5B)].

**Application to COVID-19:** 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 [[94](#ref-1037p4Gvs)]. In phase 1 and 1/2 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 [[94](#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 [[95](#ref-2bBVSpM)].

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 [[96](#ref-3KMxmQhV)] and it has subsequently been administered in Russia and other countries.

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” [[97](#ref-D3Px25HN),[98](#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 [[26](#ref-10UC562ga),[99](#ref-pWf2T8J8)]. 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 [[100](#ref-gOOBv1MD)]. JNJ-78436735 was selected from among a number of initial candidate designs [[26](#ref-10UC562ga)] and tested *in vivo* in Syrian golden hamsters and Rhesus macaques to assess safety and immunogenicity [[26](#ref-10UC562ga),[100](#ref-gOOBv1MD),[101](#ref-HmMIiIv2),[102](#ref-EpOXYGt4)]. The JNJ-78436735 candidate was selected for its favorable immunogenicity profile and ease of manufacturability [[26](#ref-10UC562ga),[100](#ref-gOOBv1MD),[101](#ref-HmMIiIv2),[102](#ref-EpOXYGt4)] and was found to confer protection against SARS-CoV-2 in macaques even after six months [[103](#ref-HGVDPMLm)]. The one- versus two-dose regimen was tested in volunteers through a phase 1/2a trial [[99](#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 [[99](#ref-pWf2T8J8)].

The three viral-vector vaccines described above have demonstrated the potential for this technology to facilitate a quick response to an emerging pathogen. 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. How these differences in design influence the efficacy of these three viral-vector vaccines over time remains to be seen.

**Trial Estimates of Safety and Efficacy:** The first DNA viral-vectored vaccine for which efficacy estimates became available was AstraZeneca’s ChAdOx1 nCoV-19. In December 2020, preliminary results of the phase 3 trial were released detailing randomized control trials conducted in the U.K., Brazil, and South Africa between April and November 2020 [[10](#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%. For Sputnik V, the phase 3 trial indicated an overall vaccine efficacy of 91.6% for symptomatic COVID-19 [[104](#ref-gLAIyAHm)]. As for Janssen, in February 2021, the FDA issued an EUA based on interim results from the phase 3 trial [[105](#ref-iWMHpTBJ),[106](#ref-1FcpboRMm)] The vaccine was well-tolerated, and across all regions studied, it was found to be 66.9% effective after 28 days for the prevention of moderate to severe COVID-19 and to be 81.7% effective for the prevention of laboratory-confirmed severe COVID-19 [[107](#ref-GOZYHZz0)]. There were no COVID-19-associated deaths in the vaccine group. However, the emergence of the beta variant in the South African trial population was associated with a slightly reduced efficacy (64% two weeks after receipt), and all of the COVID-19-associated deaths in the trial occurred in the South African placebo cohort [[107](#ref-GOZYHZz0)].

However, two of the three vaccines have faced a number of criticisms surrounding the implementation of their clinical trials. 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 [[96](#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 [[96](#ref-3KMxmQhV),[108](#ref-15DiM98Ae),[109](#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 [[96](#ref-3KMxmQhV)]. Almost a month later, the phase I/II trial data was published [[110](#ref-PNZEiId1)]

**Real-World Safety and Efficacy:** As of May 17, 2022, 3 viral-vectored vaccines are being distributed in 194 countries (Figure [3](#fig:nrvv-distrib)). ChAdOx1 nCoV-19 was first approved for emergency use on December 30, 2020 in the United Kingdom [[111](#ref-1A7PjhDDR)] and has since then been approved for emergency use in several dozen countries, in addition to receiving full approval in Brazil.

![Figure 3: Worldwide availability of vaccines developed using non-replicating viral vectors. This figure reflects the number of vaccines using non-replicating viral vectors that were available in each country as of May 17, 2022. These data are retrieved from Our World in Data <!-To Do: Cite–> and plotted using geopandas. See https://greenelab.github.io/covid19-review/ for the most recent version of this figure, which is updated daily.](data:text/html; charset=utf-8;base64,)

Figure 3: **Worldwide availability of vaccines developed using non-replicating viral vectors.** This figure reflects the number of vaccines using non-replicating viral vectors that were available in each country as of May 17, 2022. These data are retrieved from Our World in Data <!-To Do: Cite–> and plotted using geopandas. See https://greenelab.github.io/covid19-review/ for the most recent version of this figure, which is updated daily.

As of early January, Sputnik V had been administered to as many as 1.5 million Russians [[112](#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 [[113](#ref-16LczMwFO),[114](#ref-Z0V7NK7Y),[115](#ref-16GYKbrOq)], with the Czech Republic and Austria also having expressed interest in its procurement [[116](#ref-125VEHWS7)]. It wasn’t until February 2021, six months after its approval in Russia, that interim results of the phase 3 trial were released [[104](#ref-gLAIyAHm)].

#### 0.5.0.4 RNA Vaccines

Table 2: Approved RNA vaccines [[44](#ref-jswAyWIs)]

| Vaccine | Company |
| --- | --- |
| Spikevax | Moderna |
| Comirnaty | Pfizer/BioNTech |
| TAK-919 (Moderna formulation) | Takeda |

**Mechanism:** Building on DNA vaccine technology, RNA vaccines are an even more recent advancement for vaccine development. Interest in messenger RNA (mRNA) vaccines emerged around 1990 following *in vitro* and animal model studies that demonstrated that mRNA could be transferred into cells [[117](#ref-D7ou3S22),[118](#ref-2YZ70C2y)]. mRNA contains the minimum information needed to create a protein [[118](#ref-2YZ70C2y)]. RNA vaccines are therefore nucleic-acid based modalities that code for viral antigens against which the human body elicits a humoral and cellular immune response. 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 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 [[118](#ref-2YZ70C2y),[119](#ref-ENBWnhAh)].

The mRNA technology is transcribed *in vitro* and delivered to cells via lipid nanoparticles (LNP) [[120](#ref-HCImhzy8)]. They are recognized by ribosomes *in vivo* and then translated and modified into functional proteins [[121](#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 [[121](#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 [[122](#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 [[121](#ref-K0Ltu31S),[123](#ref-pRoqjur8)].

There are three types of RNA vaccines: non-replicating, *in vivo* self-replicating, and *in vitro* dendritic cell non-replicating [[124](#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 [[121](#ref-K0Ltu31S),[123](#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 [[121](#ref-K0Ltu31S)]. Self-replicating vaccines produce more viral antigens over a longer period of time, thereby evoking a more robust immune response [[124](#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 [[125](#ref-3LMMW7F0)]. These cells are isolated from the patient, grown and transfected *ex vivo*, and reintroduced to the patient [[119](#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 [[126](#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 [[121](#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 [[127](#ref-3EUiWZdN)]. Preclinical data previously identified effective antibody generation against full-length FPLC-purified influenza hemagglutinin stalk-encoding mRNA in mice, rabbits, and ferrets [[128](#ref-6wZy2mn8)]. Similar immunological responses for mRNA vaccines were observed in humans in phase 1 and 2 clinical trials operated by the pharmaceutical-development companies Curevac and Moderna for rabies, flu, and zika [[123](#ref-pRoqjur8)]. Positively charged bilayer LNPs carrying the mRNA attract negatively charged cell membranes, endocytose into the cytoplasm [[122](#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 [[122](#ref-zNKWlCwE),[129](#ref-Djz8x39x)]. Therefore, this technology holds great potential for targeted delivery of modified mRNA.

**Prior Applications:** mRNA vaccine technology was even slower to develop due to challenges related to the instability of mRNA molecules, the design requirements of an efficient delivery system, and the potential for mRNA to elicit either a very strong immune response or to stimulate the immune system in secondary ways [[35](#ref-kqerKJKY),[130](#ref-17lluDFcc)]. As of the 2010s, mRNA was still considered a promising technology for future advances in vaccine development [[118](#ref-2YZ70C2y)], but prior to 2020, no mRNA vaccines had been approved for use in humans, despite significant advances in the development of this technology [[119](#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.

**Application to COVID-19:** Given the potential for this technology to be quickly adapted for a new pathogen, it was favored as a potential vaccine against COVID-19. In the vaccines developed under this approach, the mRNA coding for a stabilized prefusion spike protein, which is immunogenic [[131](#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 3 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 [[132](#ref-1CsCQi9wT),[133](#ref-10VyxCgQU)]. The second mRNA vaccine, mRNA-1273 developed by ModernaTX, is comprised by a conventional lipid nanoparticle encapsulated RNA encoding a full-length prefusion stabilized S protein for SARS-CoV-2 [[134](#ref-Biu1CQeQ)]. As of May 17, 2022, 2 mRNA vaccines are available in 168 countries (Figure [4](#fig:mRNA-distrib)).

![Figure 4: Worldwide availability of vaccines developed using mRNA. This figure reflects the number of vaccines based on mRNA technology that were available in each country as of May 17, 2022. These data are retrieved from Our World in Data <!-To Do: Cite–> and plotted using geopandas. See https://greenelab.github.io/covid19-review/ for the most recent version of this figure, which is updated daily.](data:text/html; charset=utf-8;base64,)

Figure 4: **Worldwide availability of vaccines developed using mRNA.** This figure reflects the number of vaccines based on mRNA technology that were available in each country as of May 17, 2022. These data are retrieved from Our World in Data <!-To Do: Cite–> and plotted using geopandas. See https://greenelab.github.io/covid19-review/ for the most recent version of this figure, which is updated daily.

**Efficacy Estimates:** Pfizer/BioNTech’s BNT162b2 vaccine and ModernaTX’s mRNA-1273 vaccine, commercially known as Comirnaty and Spikevax, are available in most countries thanks to their rapid development in 2020. In a phase 2/3 multinational trial, the Pfizer/BioNTech’s BNT162b2 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 AEs when the prime-boost doses were administered 21 days apart [[135](#ref-CWlYjjIV)]. The ModernaTX mRNA-1273 vaccine was the second mRNA vaccine to release phase 3 results, despite being the first mRNA vaccine to enter phase 1 clinical trials and publish interim results of their phase 3 trial a few months later. Their study reported a 94.5% vaccine efficacy in preventing symptomatic COVID-19 in adults who received the vaccine at 99 sites around the United States [[136](#ref-ZYxoabEm)]. Similar to BNT162b2, the mRNA-1273 vaccine was associated with mild-to-moderate AEs but with a low risk of serious AEs [[136](#ref-ZYxoabEm)]. Extended details of the initial phase 1, 2, and 3 trials for both vaccines are documented in the appendix.

In late 2020, both vaccines received approval from the United States’s Food and Drug Administration (FDA) under an emergency use authorization [[137](#ref-cAaN4Te0),[138](#ref-13Ou1UUAd)], and these vaccines have been widely distributed, primarily in North America and the European Union [[139](#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.

Between December 2020 and April 2021, one prospective cohort study obtained weekly nasal swabs from 3,975 individuals at high risk of SARS-CoV-2 exposure (health care workers, frontline workers, etc.) within the United States [[140](#ref-D2ZCK63Y)]. Among these participants, 3,179 (80%) had received at least one dose of an mRNA vaccine and 2,686 (84%) were fully vaccinated. For each vaccinated participant (defined here as having received at least dose 1 more than 7 days ago) whose sample tested positive for SARS-CoV-2, they categorized the viral lineage(s) present in the sample as well as in samples from 3-4 unvaccinated individuals matched by site and testing date. Overall efficacy of mRNA vaccines was estimated at 91% with full vaccination, similar to the reports from the clinical trials. The occurrence of fevers was also lower in individuals who were partially or fully vaccinated, and the duration of symptoms was approximately 6 days shorter.

Just like the other available COVID-19 vaccines, the efficacy of mRNA vaccines has been challenged by the emergence of variants of concern (VOC). These VOC have gene mutations that code for an altered spike protein, so the antibodies developed resulting from the immunization with the existing vaccines may not be as efficacious, which has caused major concern [[141](#ref-1B4h40dm5),[142](#ref-yqFoGUHl)]. Despite some reports of varying and reduced efficacy of the mRNA vaccines against the Alpha (B.1.1.7), Beta (B.1.351), and Delta (B.1.617.2) variants versus the original SARS-CoV-2 strain or the D614G variant [[[143](#ref-x5yLFKk8)]; [[144](#ref-19dwMfMGe)]; [[145](#ref-63wnlBQD)]; ], the greatest concern to date has been the Omicron variant (B.1.1.529), which was first identified in November 2021 [[142](#ref-yqFoGUHl),[146](#ref-k7L0WGEM)]. As of March 2022, the Omicron variant accounts for 95% of all infections sequenced in the United States [[147](#ref-1Bv67ENp2)] and has been linked to an increased risk of SARS-CoV-2 reinfection [[141](#ref-1B4h40dm5)] and further infection of those who have been vaccinated with the mRNA vaccines [[148](#ref-lexoTbIa)].

Some of the gene mutations carried by Omicron, of which there are between 30-37 in the spike gene (15 in the RBD), have previously been associated with increased transmission, greater affinity for ACE2, and escape from neutralizing antibodies when they have been detected in other VOC [[141](#ref-1B4h40dm5),[142](#ref-yqFoGUHl),[149](#ref-ShwY7D1w),[150](#ref-NdeC7q3I),[150](#ref-NdeC7q3I),[151](#ref-gZ33CJWT)]. However, multiple animal study preprints suggested that the Omicron variant may not be as severe on the respiratory system as previous SARS-CoV-2 variants as evidenced by reduced lung infectivity, reduced SARS-CoV-2 RNA detection in the lung, and reduced inflammation and pathogenicity in animals [[152](#ref-15KUK3sd0),[153](#ref-145MiyjYY),[154](#ref-SV2JRcve),[155](#ref-1HYW5pt3H),[156](#ref-SgbvE4fa)].

In spite of these findings, infection rates and hospitalization rates climbed in early 2022 in many Western countries including the United States [[157](#ref-19qv58Mv3),[158](#ref-TkFSco2t)]. Studies have reported reduced efficacy of the mRNA vaccines based on the measurement of antibody titers. Plasma from individuals double-dosed with Pfizer/BioNTech’s BNT162b2 vaccine had up to a 16-fold reduction in neutralizing capacity against the Omicron variant [[151](#ref-gZ33CJWT)] and a reduced efficacy (70%) [[159](#ref-S6RHdOTJ)]. Estimates for the mRNA vaccines range from a 2-fold to over a 20-fold drop in neutralisation titers [[160](#ref-j172syOP)], hence the push for third doses of mRNA vaccines in many Western countries. A third mRNA vaccine dose does increase antibody titers, but these levels also wane with time [[161](#ref-vJlYzFrS)]. Notably, immunocompromised individuals such as cancer patients seem to elicit a sufficient protective immune response against the Omicron variant when they have been boosted with a third dose of either mRNA vaccine, albeit a blunted response [[162](#ref-sNDCRMQ5)]. While antibody titers do correlate with protection [[163](#ref-J069om3D),[164](#ref-1AtNPSzpd),[165](#ref-QYbPf88B),[166](#ref-1HCZbWd9m),[167](#ref-4WhXhBth)], they are not the only mechanisms of immune protection; for example, T cell and non-neutralizing antibody responses may be unaffected or less affected by the new VOC and they warrant further investigation.

In countries such as Israel, a fourth dose of mRNA vaccines have been introduced in response to the Omicron variant and an initial study in healthcare workers show that the additional immunization is safe and immunogenic with antibody titers restored to peak-third dose titers. No severe illness was reported in the cohort studied (274 versus 426 age-matched controls), and vaccine efficacy against infection was reported at 30% for BNT162b2 and 11% for mRNA-1273 [[168](#ref-Jv71MaZb)]. Low efficacy against infection is not surprising considering the vaccines are intended to prevent against severe disease, hospitalization and death rather than infection.

Vaccine efficacy is not the only pharmacological intervention affected by VOC. Some existing therapeutics, including monoclonal antibody treatments like Bamlanivimab (AbCellera Biologics/ Eli Lilly), were ineffective against the Omicron variant. Indeed, only Sotrovimab (Vir Biotechnology/GSK) and Tixagevimab (AstraZeneca) to a much lesser extent could effectively neutralize the omicron variant out of 7 tested monoclonal antibodies [[151](#ref-gZ33CJWT)], which has been verified by others [[150](#ref-NdeC7q3I)]. The antigenic shift of the Omicron variant does raise concerns for future VOC and what effects they may have on future vaccines and therapeutics.

**Serological Response/Boosters:**

**Variants:**

## 0.6 Special Populations

## 0.7 Effect of Vaccines on Community Spread

The vaccine clinical trial data demonstrate a significant reduction in the likelihood of contracting symptomatic COVID-19, thereby succeeding in the primary goal of vaccination. The mRNA vaccines in particular are so effective in preventing severe disease and death that it is also worth considering whether they might reduce disease transmission, given that vaccination rates are unlikely to reach 100%. This question hinges on whether vaccinated individuals with or without symptoms of COVID-19 can still spread SARS-CoV-2. This question is made up of several components. The crux is whether vaccinated individuals with a SARS-CoV-2 infection, regardless of symptom status, are as contagious as unvaccinated, infected individuals. Additionally, as outlined above, an important qualification is that the variants of SARS-CoV-2 circulating at the time of each study must be considered in light of the effect of evolution on vaccine efficacy.

The phase 2/3 clinical trials evaluating the mRNA vaccines assessed vaccine efficacy based on COVID-19 diagnosis, thereby detecting only patients who received a diagnosis. In order to identify patients infected with SARS-CoV-2 who did not receive a diagnosis, for example, potentially those who did not develop symptoms, it would be necessary to conduct routine PCR testing even in the absence of symptoms. Prior to the development of vaccines, the evidence suggested that asymptomatic individuals could still spread SARS-CoV-2. Investigation of viral dynamics of asymptomatic infection in early 2020 indicated that asymptomatic patients continued to shed the virus for a duration similar to that of symptomatic patients [[169](#ref-ZU1ZF4SW)] (although viral shedding should not be conflated with contagiousness without further investigation [[7](#ref-GdZc4Yyd)]). Another study found viral load to be higher in the nasopharyngeal/oropharyngeal samples of asymptomatic patients compared to symptomatic patients hospitalized due to symptoms and/or known exposure [[170](#ref-whGzxrkn)]. However, the sample size in both of these studies was small, and a larger study found higher viral load in symptomatic than asymptomatic cases [[171](#ref-34wAjHW5)] along with a systematic review finding a reduced probability of asymptomatic transmission [[172](#ref-1CA0Sj7dn)]. While far from conclusive, these studies suggest that asymptomatic cases still cary a risk of transmitting SARS-CoV-2.

One important consideration is therefore how likely vaccinated individuals are to develop asymptomatic SARS-CoV-2. Considering asymptomatic cases is necessary to establish a more complete picture of efficacy with respect to spread. Routine testing of healthcare workers in California who had received an mRNA vaccine revealed slightly higher rates of absolute risk for testing positive than those identified in the phase 2/3 trials, although the extent to which asymptomatic infection influenced these numbers was not investigated [[173](#ref-13llzZ2qN)]. Another study analyzed the results of COVID-19 screening tests administered to asymptomatic individuals prior to receiving certain medical services at the Mayo Clinic in several locations across the United States. This study found patients who had received two doses of an mRNA vaccine to be 73% less likely to have asymptomatic COVID-19 than patients who had received zero doses [[174](#ref-dLmXTkx0)]. Because this study began on December 17, 2020, a date selected to coincide with the first day vaccines were available at the Mayo Clinic, this number may underestimate the efficacy of the vaccines given that many people eligible for early vaccination were at increased risk for exposure (e.g., healthcare workers and residents of long-term care facilities) [[174](#ref-dLmXTkx0)]. In Israel, a longitudinal study of nearly 12,000 healthcare workers found that of the 5,372 fully vaccinated people with Pfizer/BioNTech BNT162b2, 8 developed symptomatic COVID-19 (BNT162b2 (.15%) and 19 developed asymptomatic COVID-19 (.35%) [[175](#ref-zHE6Quu6)]. While the study itself analyzed the efficacy of the vaccine based on person-days, these findings also suggest that many or even the majority of SARS-CoV-2 infections in vaccinated individuals are likely to be asymptomatic. Therefore, in addition to the symptomatic cases reported by the vaccine clinical trials, these findings suggest that asymptomatic cases can also occur in vaccinated people. In the absence of symptoms, individuals are less likely to know to self-isolate, and therefore evaluating the effect of the vaccine on viral load is critical to understanding the role vaccinated individuals can play in spreading SARS-CoV-2.

Another question of interest is therefore whether vaccinated individuals positive for SARS-CoV-2 carry a similar viral load to unvaccinated individuals. Viral load is often approximated by cycle threshold (Ct), or the cycle at which viral presence is detected during RT-qPCR, with a lower Ct corresponding to a greater viral load. A prospective cohort study that evaluated front-line workers in six U.S. states from December 2020 to April 2021 reported a 40% reduction in viral load even with just a single dose of an mRNA vaccine [[140](#ref-D2ZCK63Y)]. The vaccine also appeared to influence the time to viral clearance: the risk of having detectable levels of SARS-CoV-2 for more than one week was reduced by 66% in participants who had received at least one dose [[140](#ref-D2ZCK63Y)]. However, this study compared the mean viral load across the two groups, meaning that these findings cannot be extrapolated across all points in the disease course. Similarly, between December 2020 and February 2021, positive RT-qPCR tests were analyzed for almost 5,000 Israeli patients [[176](#ref-119cExL0k)]. Ct was analyzed relative to when each patient received the first dose of the Pfizer mRNA vaccine. A sharp increase in Ct (corresponding to reduced viral load) was observed between days 11 and 12, consistent with what is known about the onset of immunity following vaccination. This pattern therefore suggested a direct effect of vaccination on viral load.

Other studies, however, have not offered support for a reduced viral load in breakthrough cases. In Singapore, which has strict protocols for screening individuals with potential COVID-19 exposure, a retrospective cohort of patients who tested positive for SARS-CoV-2 between April and June 2021 was analyzed to compare viral kinetics and symptom course between vaccinated and unvaccinated cases. Vaccinated individuals who tested positive experienced fewer symptoms than unvaccinated, SARS-CoV-2-positive individuals and were more likely to be asymptomatic [[177](#ref-e2Qnnj6R)] (Appendix). Additionally, this study analyzed Ct over time and found that, though the median values were similar between the two groups at disease onset, viral load appeared to decrease more rapidly in vaccinated cases [[177](#ref-e2Qnnj6R)] (Appendix). This study is likely to have evaluated a more accurate representation of all COVID-19 outcomes than has been feasible in most studies, but one limitation was that the RT-PCR reactions were conducted in many different facilities. A third study investigated viral load (as approximated by Ct) using samples processed in a single laboratory during the summer of 2021 [[178](#ref-N5OXLf7V)]. This study identified no significant differences in Ct between fully vaccinated and unvaccinated cases, but this study used samples sent for diagnosis and was not longitudinal. It offered the additional benefit of culturing samples to assess whether their Ct threshold was likely to represent contagiousness and found that SARS-CoV-2 could be cultured from 51 of 55 samples with Ct less than 25 (the cut-off used in many studies). Another study of samples collected at two sites in San Francisco, one of which tested only asymptomatic individuals, reported no difference in Ct between asymptomatic and symptomatic cases regardless of whether vaccination status was included in the model [[179](#ref-mgscHeDu)]. Though each of these three studies offers distinct strengths and weaknesses, taken together, they suggest that viral load is likely to be similar in vaccinated and unvaccinated individuals, but that vaccinated individuals clear the virus more rapidly, meaning that the average viral load is lower over time.

Given the emergence of variants of concern, especially the Delta variant, for which breakthrough infections are more common, the potential for vaccinated individuals to spread SARS-CoV-2 is not necessarily static over time. In fact, studies reporting reduced viral load in vaccinated individuals collected samples, for the most part, prior to the emergence of the Delta variant’s dominance. The emergence of this variant may partially account for why more recent studies tend to find no difference between viral load in vaccinated and unvaccinated cases.

Taken together, these findings can provide some insight into how vaccines influence community spread. While vaccinated individuals may be more likely to experience asymptomatic infection, current evidence about viral load in asymptomatic versus symptomatic cases is ambiguous. Similarly, no conclusions can be drawn about whether viral load is different in vaccinated versus unvaccinated cases. Therefore, at present, the evidence suggests that vaccinated individuals who are infected can still contribute to community spread. The one potential mitigating factor supported at present is that differences in the viral kinetics may result in vaccinated cases infecting fewer individuals over time due to a more rapid decrease in viral load [[177](#ref-e2Qnnj6R)], although this study did not examine patterns in secondary transmission. Thus, the virological evidence suggests that public health measures such as masking and distancing remain important even in areas with high vaccination rates.

### 0.7.1 Other Concerns in Efficacy

Efficacy estimates have been released for many vaccine candidates across a number of technology types. However, efficacy is not a static value, and real-world efficacy can vary with location and over time. Temporal shifts in efficacy have been a especially heightened topic of concern in late 2021 given the potential for the evolution of SARS-CoV-2 to influence vaccine efficacy. The original efficacy estimates are outlined in Table XX and additional considerations for each vaccine type are described in more detail below.

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. CoronaVac appears to be suitable for use in immunocompromised patients such as those with autoimmune rheumatic diseases according to phase 4 trials [[180](#ref-8vzglCry)]. CoronaVac was also well tolerated and induced humoral responses in phase 1 trials in children aged 3 to 17 years, which will now be examined in phase 2 and 3 clinical trials [[181](#ref-6EYqf6s7)].

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

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

Given the apparent need for boosters, interest has also emerged in whether vaccines against SARS-CoV-2 can be administered along with annual flu vaccines. Early data came from the Novavax NVX-CoV2373 protein subunit vaccine. In a subgroup of approximately 400 patients enrolled from the U.K. phase 3 trial who received either NVX-CoV2373 or placebo 1:1, a concomitant dose of adjuvanted seasonal influenza vaccines (either a trivalent vaccine or a quadrivalent vaccine) was administered [[182](#ref-IUekaKY0)]. This study demonstrated that both types of vaccines could be safely administered together. While no change to the immune response was noted for the influenza vaccine, a notable reduction of the antibody response for the NVX-CoV2373 was reported, but efficacy was still high at 87.5% [[182](#ref-IUekaKY0)]. Novavax has since started phase 1/2 trials to investigate the administration of its own influenza vaccine, NanoFlu™, concomitantly with NVX-CoV2373 [[183](#ref-rclKBvtk)], which appeared to be safe and effective in preclinical studies [[184](#ref-bOwPRh6q)].

Indeed, Chinese [[185](#ref-9oJ3sbrk)] and Chilean [[186](#ref-uPt61a0E)] researchers have opted to investigate options to administer different vaccines (e.g., an mRNA vaccine dose) as a booster dose to individuals who have already received two doses of the IWV vaccine CoronaVac. Another study has already determined that using the CanSino vaccine (Convidecia) instead of CoronaVac in a prime-boost vaccination regimen can induce a more robust immune response [[187](#ref-1HVWY0Qmv)].

## 0.8 Conclusions

In the early 2000s, technologies such as inactivated viral vaccines, live attenuated viral vaccines, protein subunit vaccines, and recombinant vector-based vaccines were explored for SARS [[188](#ref-H4USOXie),[189](#ref-AOGjkjCq)], but the epidemic was controlled before these efforts came to fruition [[3](#ref-HyYY2agc)]. DNA vaccine development efforts also began but did not proceed past animal testing [[189](#ref-AOGjkjCq)]. Similarly, viral vector, protein subunit, and DNA vaccines were explored for MERS-CoV, but outbreaks are sporadic and difficult to predict, making vaccine testing and the development of a vaccination strategy difficult [[190](#ref-138O0v19T)]. Likewise, the development of viral-vectored Ebola virus vaccines was undertaken, but the pace of vaccine development was behind the spread of the virus from early on [[191](#ref-vTrIB9zS)]. Although a candidate Ebola vaccine V920 showed promise in preclinical and clinical testing, it did not receive breakthrough therapy designation until the summer of 2016, by which time the Ebola outbreak was winding down [[192](#ref-8uuVgxzA)].

This vaccine uses a plasmid to deliver the expression-competent Spike protein and IgE signal peptides to the vacinee [[193](#ref-1CCmltPec)]. During the phase 1 trial, vaccination with a needle versus syringe was evaluated, and the vaccine can now be administered without a needle [[50](#ref-AfMvzFuk),[51](#ref-eIn1Qf3N)]. This highly portable design offers advantages over traditional vaccines [[**doi10.1016/j.eclinm.2021.101020?**](#ref-doi10.1016/j.eclinm.2021.101020)].

# 1 Additional Items

## 1.1 Competing Interests

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

## 1.2 Author Contributions

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

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