The Coming of Age of Nucleic Acid Vaccines during COVID-19

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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. Their importance has been made especially clear by 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 against this virus at an unprecedented pace. Part of this success was attributable to broader shifts in scientific research relative to prior epidemics. For example, 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. Additionally, however, 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 the development of COVID-19 vaccines relative to prior efforts to apply these technologies. We describe where these candidates currently stand in terms of efficacy, safety, and approval and discuss patterns in worldwide distribution. The advances made since early 2020 provide 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 demands on but also opportunities for vaccine developers. As of August 10, 2022, there have been over 587,493,309 SARS-CoV-2 cases, and it has taken the lives of at least 6,427,446 people globally. The development, production, and distribution of vaccines is imperative to saving lives, preventing severe illness, and reducing the economic and social burdens caused by the COVID-19 pandemic. Although these vaccine technologies had never previously been approved for use in humans, they have played a leading role in the management of SARS-CoV-2. In this review we discuss the history of developing these vaccines and how they have been applied to 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 SARS-CoV-2 virus emerged at the end of 2019 and quickly spread around the world. One of the primary approaches available to combat the effects of a virus is vaccination. Vaccines bolster the immune response to the virus at the individual and population level, thereby significantly reducing fatalities and severe illness and potentially driving a lower rate of infection even for a highly infectious virus like SARS-CoV-2. However, vaccine development has historically been slow.

As we review in a companion manuscript [[1](#ref-S1SpDOhi)], vaccine technologies have largely been based on introducing a virus or a component of a virus that is sufficient to induce an immune response without causing the associated illness. 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. This shift towards nucleic acid-based technologies opens a new frontier in vaccinology, where just the sequence encoding an antigen can be introduced to induce an immune response. While other platforms introduce viral components that can in some cases present risks of infection, nucleic acid-based platforms eliminate these risks. Additionally, 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.

## 0.4 Honing a 21st Century Response to Emergent Viral Threats

Recently, vaccine technologies have been developed and refined in response to several epidemics that did not reach the level of destruction caused by COVID-19. Emergent viral threats of the 21st century include severe acute respiratory syndrome (SARS), “swine flu” (H1N1 influenza), Middle East respiratory syndrome (MERS), Ebola virus disease (EVD), COVID-19, and monkeypox, 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 [[2](#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 of America (U.S.A.) 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.

Efforts to develop such approaches have been undertaken prior to the COVID-19 pandemic. DNA vaccine development efforts began for SARS-CoV-1 but did not proceed past animal testing [[4](#ref-AOGjkjCq)]. 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 [[5](#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 [[6](#ref-8uuVgxzA)].

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 presented a global threat for such a sustained duration (see visualization in [[7](#ref-njpLhBui)]). 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 [[8](#ref-GdZc4Yyd)]. 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.

## 0.5 Development of COVID-19 Vaccines using DNA and RNA Platforms

Vaccine development programs for COVID-19 emerged very quickly. The first administration of a dose of a COVID-19 vaccine to a human trial participant occurred on March 16, 2020 [[9](#ref-fQvzeptv),[10](#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 [[10](#ref-1GA95MF2m)], and by September 2020, there were over 180 vaccine candidates against SARS-CoV-2 in development [[11](#ref-dqpEe5Lz)]. As of August 11, 2022, 40 SARS-CoV-2 vaccines have been approved world wide and 29 are being administered throughout the world, with doses administered across 223 countries. 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 [[12](#ref-vlGP3RAU)]. 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 [[13](#ref-Vnbw9o3T),[14](#ref-13wCBLnnu)].



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.com, and the microscopy image is from the National Institute of Allergy and Infectious Diseases Integrated Research Facility [[15](#ref-Jzj97hJh)].

During the development process, one measure used to assess whether a vaccine candidate is likely to provide protection is serum neutralizing activity [[16](#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 also test vaccines in phase III trials where the effect of the vaccines on a cohort’s likelihood of contracting SARS-CoV-2 was evaluated. The Coalition for Epidemic Preparedness Innovations (CEPI) is coordinating global health agencies and pharmaceutical companies to develop vaccines against SARS-CoV-2.

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. In many cases, SARS-CoV-2 is the first pathogen for which these technologies have been approved and administered widely. These programs employ a variety of technologies, ranging from established approaches to novel technologies that had never previously gone to market. Development programs using more established technologies are reviewed in a companion manuscript. Here, we review the various technologies being explored for the development of SARS-CoV-2 vaccines that use technologies based on nucleic acids.

## 0.6 Cross-Platform Considerations in Vaccine Development

Certain design decisions are relevant to vaccine development across multiple platforms. One applies to the platforms that deliver the antigen, which in the case of SARS-CoV-2 vaccines is the S protein. The prefusion conformation of the S protein, which is the structure before the virus fuses to the host cell membrane, is metastable [[17](#ref-R7Xdh5nH)], and the release of energy during membrane fusion drives this process forward following destabilization [[18](#ref-17DSmRo9H),[19](#ref-3uddYea8)]. Due to the significant conformational changes that occur during membrane fusion [[20](#ref-qcVbT0w4),[21](#ref-hIc3bKWe),[22](#ref-zK0rFpz1)], S protein immunogens that are stabilized in the prefusion conformation are of particular interest, especially because a prefusion stabilized *Middle East respiratory syndrome-related coronavirus* (MERS-CoV) S antigen was found to elicit an improved antibody response [[23](#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 [[23](#ref-oghHqZDt),[24](#ref-13wWdgODZ),[25](#ref-OVsxrEuX)] (see also [[8](#ref-GdZc4Yyd)]). Vaccine developers can stabilize the prefusion conformer by selecting versions of the S protein containing mutations that lock the position [[26](#ref-lvq9hGmj)]. The immune response to the spike protein when it is stabilized in this conformation is improved over other S structures [[27](#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 [[28](#ref-13bVbfc5h),[29](#ref-122h6fIxE),[30](#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 [[31](#ref-17qiILENK)]. To date, the most significant variants of concern identified are Alpha (2020), Beta (2020), Gamma (2020), Delta (2021), Omicron (2021), and related Omicron subvariants (2022). The efficacy of vaccines in the context of these variants is discussed where information is available.

## 0.7 Theory and Implementation of Nucleic Acid Vaccines

Biomedical research in the 21st century has been significantly influenced by the genomic revolution. While traditional methods of vaccine development, such as inactivated whole viruses are still used today [[1](#ref-S1SpDOhi)], vaccine development is no exception. The shift towards omics-based approaches to vaccine development began to take hold with the meningococcal type B vaccine, which was developed using reverse vaccinology in the early 2010s [[32](#ref-MCZBJ5sF),[33](#ref-fw8IwtHq)]. In this way, the genomic revolution catalyzed a fundamental shift in the development of vaccines. Such technologies could revolutionize the role of vaccines given their potential to address one of the major limitations of vaccines today and facilitate the design of therapeutic, rather than just prophylactic, vaccines [[34](#ref-kqerKJKY)].

Nucleic-acid based approaches share an underlying principle: a vector that delivers the information needed to produce an antigen. When the host cells manufacture the antigen, it can then trigger an immune response. The fact that no part of the virus is introduced aside from the genetic code of the antigen makes these platforms very safe. 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* [[35](#ref-YY3x3bBV)]. Studies also demonstrated that model organisms could be induced to construct antigens that would trigger an immune response [[36](#ref-U9ZIZWkB),[37](#ref-pWMIo6pD),[38](#ref-uPszIvSj)]. These two developments sparked interest in whether 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.

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 [[39](#ref-BsrTDzJ2)]. Delivering a nucleic acid sequence to host cells allows the host to synthesize an antigen without exposure to a viral threat [[39](#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 [[39](#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 [[39](#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.

In nucleic-acid-based approaches, the genome of a pathogen is screened to identify potential vaccine targets [[33](#ref-fw8IwtHq)], and pathogens of interest are then expressed *in vitro* and tested in animal models to determine their immunogenicity [[33](#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 [[38](#ref-uPszIvSj)]. This dual presentation means that both humoral and cellular immunity are activated [[39](#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 [[39](#ref-BsrTDzJ2),[41](#ref-29LxSWHB)].

## 0.8 DNA Vaccine Platforms

DNA vaccine technologies have developed slowly over the past thirty years. DNA vaccines introduce a vector containing a DNA sequence that encodes the antigen(s) necessary to induce a specific immune response into appropriate tissues where *in situ* expression of the target antigen is induced [[38](#ref-uPszIvSj)]. Early attempts revealed issues with low immunogenicity [[36](#ref-U9ZIZWkB),[38](#ref-uPszIvSj),[42](#ref-12jFcMeQY)]. Additionally, initial skepticism about the approach suggested that DNA vaccines might bind to the host genome or induce autoimmune disease [[39](#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)]. These safety concerns 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 [[39](#ref-BsrTDzJ2)]. While this issue was resolved through strategic vector design [[43](#ref-Wjtx0VXu),[44](#ref-5fcD0JWR)], the immunogenicity of these vaccines did not reach expectations [[39](#ref-BsrTDzJ2)].

Several developments during the 2010s led to greater efficacy of DNA vaccines [[39](#ref-BsrTDzJ2)]. However, no DNA vaccines had been approved for use in humans prior to the COVID-19 pandemic [[42](#ref-12jFcMeQY),[45](#ref-yriARFOF)]. As of August 12, 2022, XX vaccines have been approved worldwide (Table [1](#tbl:approved-DNA)). These vaccines fall into two categories, vaccines that are vectored with a plasmid and those that are vectored with another virus.

Table 1: Approved DNA vaccines [[46](#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 |

### 0.8.1 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 [[47](#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 [[38](#ref-uPszIvSj),[44](#ref-5fcD0JWR)]. Once the plasmid 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 [[39](#ref-BsrTDzJ2)]. The vectors are edited to remove extra sequences [[44](#ref-5fcD0JWR)]. These types of manufacturing advances have improved the safety and throughput of this platform [[44](#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 [[39](#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 [[39](#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 [[39](#ref-BsrTDzJ2)].

Early plasmid-vectored DNA vaccine trials targeted HIV and subsequently diseases of worldwide importance such as malaria and hepatitis B [[48](#ref-3EKs730C)]. The concern with these early development projects was immunogenicity, not safety [[48](#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 [[49](#ref-jPpzjaYO)]. As of 2018, however, only two plasmid-vectored DNA vaccines had been approved for commercial use, and both were for veterinary populations [[50](#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 [[51](#ref-AfMvzFuk),[52](#ref-eIn1Qf3N)].

Similarly, another plasmid-vectored DNA vaccine, INO-4800 [[53](#ref-xuzLfS0y)], was developed by Inovio Pharmaceuticals Technology that uses electroporation as an adjuvant. Electroporation was developed as a solution to the issue of limited immunogenicity by increasing the permeability of cell membranes by delivering electrical pulses [[54](#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 [[55](#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® [[56](#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 [[54](#ref-1Hsm2J1sc)].

These vaccines therefore represent implementations of a new platform technology. In particular, they offer the advantage of a temperature-stable vaccine, facilitating worldwide administration [[57](#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 I 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 [[56](#ref-4xraQp8j)]. Among the 39 participants, only six AEs were reported and all were grade 1 [[56](#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 [[56](#ref-4xraQp8j)]. Results from the phase II 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 [[57](#ref-OYnqjMlC)]. The phase II 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 [[57](#ref-OYnqjMlC)]. The rates of AEs in the placebo group were not reported.

To assess the immunogenicity of INO-4800, pre- and post-vaccination blood samples were collected and 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 [[57](#ref-OYnqjMlC)]. The phase II/III trials are ongoing in several countries, including the United States, Mexico, India, and Colombia [[58](#ref-pxEE3VEQ),[59](#ref-R79Wr1hU),[60](#ref-yraL6YQa),[61](#ref-Wk6spoae)]. Therefore, vaccine efficacy data from a large study population is not yet available.

**Real-World Safety and Efficacy:** The efficacy of ZyCoV-D is estimated to be 66.6% [[62](#ref-3xlXzOoW)]. Because phase III data is not yet available for INO-4800, the VE is not yet know.

Studies have examined the ability of INO-4800 to induce an immune response that can neutralize existing VOC. They assessed neutralization of several VOC relative to the index strain [[63](#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) [[63](#ref-mbBuH8XY)]. These findings are in line with the shifts in efficacy reported for other vaccines [[1](#ref-S1SpDOhi)].

In addition to loss of neutralizing activity due to viral evolution, studies have also evaluated the decline in nAbs induced by INO-4800 over time. Levels of nAbs remained statistically significant relative to the pre-vaccination baseline for six months [[64](#ref-CSlbNoGU)]. Administration of a booster dose induced a significant increase of titers relative to their pre-booster levels [[64](#ref-CSlbNoGU)]. Given the timing of this trial (enrollment between April and July 2020), it is unlikely that participants were exposed to VOC associated with decreased efficacy.

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 [[65](#ref-ysgD4Dcf)]. Known as INO-4802, this vaccine was designed to express a pan-Spike immunogen [[66](#ref-Aynz3sBj)]. Booster studies in rodents [[67](#ref-12zreC1Tk)] and non-human primates [[66](#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 [[66](#ref-Aynz3sBj)]. Therefore, boosting is likely to be an important strategy for this vaccine, especially as the virus continues to evolve.

### 0.8.2 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 [[68](#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 [[69](#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 host can then synthesize antibodies in response [[39](#ref-BsrTDzJ2)].

One of the early viral vectors explored was adenovirus, with serotype 5 (Ad5) being particularly effective [[39](#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 [[39](#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 [[39](#ref-BsrTDzJ2),[70](#ref-XRmk1S6R)], and chimpanzee adenoviruses were explored as a potential vector in the development of a vaccine against MERS-CoV [[71](#ref-Jkm7jfS8)].

Today, various viral-vector platforms including poxviruses [[72](#ref-8bpbvIro),[73](#ref-1AZfAQ5py)], adenoviruses [[74](#ref-zX5UKhti)], and vesicular stomatitis viruses [[75](#ref-SNwg8Qkf),[76](#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 [[74](#ref-zX5UKhti),[77](#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 [[78](#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 [[78](#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 [[79](#ref-IUplTKEg)].

**Prior Applications:** There are several viral vector vaccines that are available for veterinary use [[39](#ref-BsrTDzJ2),[80](#ref-MvKb0qJC)], but prior to the COVID-19 pandemic, only one viral vector vaccine was approved by the United States’ Food and Drug Administration (FDA) for use in humans. This vaccine is vectored with a recombinant vesicular stomatitis virus and targeted against the Ebola virus [[81](#ref-9g5tmszW)]. Additionally, several phase I and phase II clinical trials for other vaccines are ongoing [[68](#ref-1Ff2BDzkT)], and the technology is currently being explored for its potential against numerous infectious diseases including malaria [[82](#ref-OZJWUaDW),[83](#ref-3tkGuMXx)], Ebola [[84](#ref-AgZwwt5u),[85](#ref-9BEMTYn8),[86](#ref-PbGQOOI)], and HIV [[87](#ref-1C8hgfvDF),[88](#ref-SAIfGNkZ)].

The threat of MERS and SARS initiated interest in the application of viral vector vaccines to human coronaviruses [[71](#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 2000s, adenoviral vectored vaccines against SARS were found to induce SARS-CoV-specific IgA in the lungs of mice [[89](#ref-umEOWDY5)] but were later found to offer incomplete protection in ferret models [[90](#ref-DGTFML2b)]. Gamaleya National Center of Epidemiology and Microbiology in Moscow sought to use an adenovirus platform for the development of vaccines for MERS-CoV and Ebola virus, although neither of the previous vaccines were internationally licensed [[91](#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 [[92](#ref-P94sxWp4)]. This study reported that a candidate containing the complete S protein sequence induced a stronger neutralizing antibody response in mice than candidates vectored with modified vaccinia virus Ankara.

The candidate 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 [[93](#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 [[94](#ref-ERfSJf5B)].

**Application to COVID-19:** While not all of the above 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 SARS-CoV-2. First, a collaboration between AstraZeneca and researchers at the University of Oxford 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 S protein of SARS-CoV-2 [[95](#ref-1037p4Gvs)]. In a phase I trial, the immunogenic potential of vaccine candidate ChAdOx1 nCoV-19 was demonstrated through the immune challenge of two animal models, mice and rhesus macaques [[95](#ref-1037p4Gvs)]. In a phase I/II trial, 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 [[96](#ref-2bBVSpM)].

Second, a viral vector approach was applied by Russia’s Gamaleya Research Institute of Epidemiology and Microbiology 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. 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 [[97](#ref-sRAZYY9C)], as some individuals may possess immunity to Ad5 [[98](#ref-8jwp261S)]. Sputnik V is the only recombinant adenovirus vaccine to utilize two vectors.

Third, Janssen Pharmaceuticals, Inc., a subsidiary of Johnson & Johnson, developed a viral vector vaccine in collaboration with and funded by the United States’ “Operation Warp Speed” [[99](#ref-D3Px25HN),[100](#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 [[27](#ref-10UC562ga),[101](#ref-pWf2T8J8)]. Unlike the other two viral vector vaccines available to date, JNJ-78436735 requires only a single dose, a characteristic that was expected to aid in global deployment [[102](#ref-gOOBv1MD)]. JNJ-78436735 was selected from among a number of initial candidate designs [[27](#ref-10UC562ga)] and tested *in vivo* in Syrian golden hamsters and Rhesus macaques to assess safety and immunogenicity [[27](#ref-10UC562ga),[102](#ref-gOOBv1MD),[103](#ref-HmMIiIv2),[104](#ref-EpOXYGt4)]. The JNJ-78436735 candidate was selected for its favorable immunogenicity profile and ease of manufacturability [[27](#ref-10UC562ga),[102](#ref-gOOBv1MD),[103](#ref-HmMIiIv2),[104](#ref-EpOXYGt4)] and was found to confer protection against SARS-CoV-2 in macaques even after six months [[105](#ref-HGVDPMLm)]. The one- versus two-dose regimen was then tested in volunteers through a phase I/IIa trial [[101](#ref-pWf2T8J8),[106](#ref-69GoEX0X)]. A major difference between this vaccine and the other two in this category is that the S protein immunogen is stabilized in its prefusion conformation, while in the Sputnik V and AstraZeneca vaccines it is not.

**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 III trial were released detailing randomized control trials conducted in the United Kingdom (U.K.), Brazil, and South Africa between April and November 2020 [[13](#ref-Vnbw9o3T)]. These trials 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 III trial indicated an overall vaccine efficacy of 91.6% for symptomatic COVID-19 [[107](#ref-gLAIyAHm)]. As for Janssen, in February 2021, the FDA issued an EUA based on interim results from the phase 3 trial [[108](#ref-iWMHpTBJ),[109](#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 [[110](#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 [[110](#ref-GOZYHZz0)].

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 11, 2020 in the absence of clinical evidence [[111](#ref-3KMxmQhV)]. A press release on November 11, 2020 indicated positive results from an interim analysis of the phase III Sputnik V trials, which reported 92% efficacy in 16,000 volunteers [[112](#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 [[112](#ref-JSzDvnk6),[113](#ref-Yzz3rwqk)]. 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 [[111](#ref-3KMxmQhV),[114](#ref-15DiM98Ae),[115](#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 [[111](#ref-3KMxmQhV)]. Almost a month later, the phase I/II trial data was published [[116](#ref-PNZEiId1)] It wasn’t until February 2021, six months after its approval in Russia, that interim results of the phase 3 trial were released [[107](#ref-gLAIyAHm)].

AstraZeneca’s clinical trial also faced criticism. The trial was paused in September 2020 following a severe adverse event in one participant [[117](#ref-vwhmuwto)]. It was restarted soon after [[118](#ref-Fz6kXAHy)], but it seems that the recent pause was not mentioned to the FDA during a call the morning before the story broke [[119](#ref-Kt4zFpsF)]. Additionally, individual sites within the trial employed somewhat different designs but were combined for analysis. 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. evaluated two dosing regimens (low dose or standard dose, both followed by standard dose). Some of the trials used a meningococcal conjugate vaccine (MenACWY) as a control, while others used saline. Data was pooled across countries for analysis, a design decision that was approved by regulators but raised some questions when higher efficacy was reported in a subgroup of patients who received a low-dose followed by a standard dose. This group came about because some participants in the U.K. were erroneously primed with a much lower dose, which turned out to have higher efficacy than the intended dose [[120](#ref-4mDUvRId)]. Combining the data then led to confusion surrounding the VE, as VE varied widely among conditions (e.g., 62% VE in the standard dose group vs 90% in the group that received a low prime dose [[13](#ref-Vnbw9o3T)]). Subsequent research, however, suggests that reducing the prime dose may, in fact, elicit a superior immune response in the long-term despite a lower initial response [[121](#ref-SUGCFKUo)]. Therefore, this error may serendipitously improve efficacy of vaccine-vectored vaccines broadly.

**Real-World Safety and Efficacy:** As of August 11, 2022, 5 viral-vectored vaccines are being distributed in 202 countries (Figure [2](#fig:nrvv-distrib)). ChAdOx1 nCoV-19 was first approved for emergency use on December 30, 2020 in the U.K. [[122](#ref-1A7PjhDDR)]. As early as January 2021, Sputnik V had been administered to 1.5 million Russians [[123](#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 [[124](#ref-16LczMwFO),[125](#ref-Z0V7NK7Y),[126](#ref-16GYKbrOq)], with the Czech Republic and Austria also having expressed interest in its procurement [[127](#ref-125VEHWS7)].



Figure 2: **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 August 11, 2022. These data are retrieved from Our World in Data [[128](#ref-sRy6js2o)] and plotted using geopandas [[129](#ref-iGEyNO42)]. See https://greenelab.github.io/covid19-review/ for the most recent version of this figure, which is updated daily.

Following the trials, additional concerns have been raised about some of these vaccines. Within a few days to a few weeks following their first dose of the AstraZeneca vaccine, three women developed extensive venous sinus thrombosis [[130](#ref-5gqQwOi6)]. In March 2021, administration of the vaccine was paused in several European countries while a possible link to thrombotic events was investigated [[131](#ref-Q4qW6ARY)], as these adverse events had not been observed in clinical trials, but the European Medicine Agency (EMA) soon determined that 25 events were not related to the vaccine [[132](#ref-xSBGseR)]. The following month, the United States paused administration of the Janssen vaccine for ten days due to 15 similar AEs [[133](#ref-TtPVfMOL),[134](#ref-1F1ma0vMT)], but the EMA, CDC, and the FDA’s Advisory Committee on Immunization Practices again identified the events as being very rare and the benefits of the vaccine as likely to outweigh its risks [[135](#ref-iRvYqPq6),[136](#ref-MnBdD0Mr),[137](#ref-2uAR3HBq),[138](#ref-EqBIFx5T)]. In Denmark and Norway, population-based estimates suggested AstraZeneca’s vaccine increased incidence of venous thromboembolic events by 11 cases over baseline per 100,000 doses [[139](#ref-tTpW7jvQ)]. Estimates of the incidence in other western countries have also been low [[140](#ref-rWaWz2Yg)]. In the US, thromboembolic events following the Janssen vaccine have also been very rare [[136](#ref-MnBdD0Mr)]. Subsequently, a potential mechanism was identified: the adenovirus vector binding to platelet factor 4 (PF4) [[141](#ref-z5vyJuGl),[142](#ref-XwlVcLVP)]. Because this adverse event is so rare, the risk is likely still outweighed by the risks associated with contracting COVID-19 [[143](#ref-itL8KsXg)], which is also associated with thrombotic events) [[134](#ref-1F1ma0vMT),[144](#ref-fcm6ElC0)]. Similarly, concerns about Guillain-Barré syndrome arose in connection to the Janssen vaccine, but these events have similarly been determined to be very rare and the benefits to outweigh the risks [[138](#ref-EqBIFx5T)].

## 0.9 RNA Vaccines

Table 2: Approved RNA vaccines [[46](#ref-jswAyWIs)]

| Vaccine | Company |
| --- | --- |
| GEMCOVAC-19 | Gennova Biopharmaceuticals Limited |
| 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 [[145](#ref-D7ou3S22),[146](#ref-2YZ70C2y)]. mRNA contains the minimum information needed to create a protein [[146](#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 [[146](#ref-2YZ70C2y),[147](#ref-ENBWnhAh)].

The mRNA is transcribed *in vitro* and delivered to cells via lipid nanoparticles (LNP) [[148](#ref-HCImhzy8)]. It is recognized by ribosomes *in vivo* and then translated and modified into functional proteins [[149](#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 [[149](#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 [[150](#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 fast performance liquid chromatography and high performance liquid chromatography technology will improve translation of the mRNA in the cell [[149](#ref-K0Ltu31S),[151](#ref-pRoqjur8)].

There are three types of RNA vaccines: non-replicating, *in vivo* self-replicating, and *in vitro* dendritic cell non-replicating [[152](#ref-1EM5nGaYd)]. Non-replicating mRNA vaccines consist of a simple open reading frame 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 [[149](#ref-K0Ltu31S),[151](#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 [[149](#ref-K0Ltu31S)]. Self-replicating vaccines produce more viral antigens over a longer period of time, thereby evoking a more robust immune response [[152](#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 [[153](#ref-3LMMW7F0)]. These cells are isolated from the patient, then grown and transfected *ex vivo* [[147](#ref-ENBWnhAh)]. They can then be reintroduced to the patient [[147](#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 [[154](#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 [[149](#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 [[155](#ref-3EUiWZdN)]. Preclinical data previously identified effective antibody generation against full-length purified influenza hemagglutinin stalk-encoding mRNA in mice, rabbits, and ferrets [[156](#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 [[151](#ref-pRoqjur8)]. Positively charged bilayer LNPs carrying the mRNA attract negatively charged cell membranes, endocytose into the cytoplasm [[150](#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 [[150](#ref-zNKWlCwE),[157](#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 [[34](#ref-kqerKJKY),[158](#ref-17lluDFcc)]. As of the 2010s, mRNA was still considered a promising technology for future advances in vaccine development [[146](#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 [[147](#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 [[159](#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 [[160](#ref-1CsCQi9wT),[161](#ref-10VyxCgQU)]. The second mRNA vaccine, mRNA-1273 developed by ModernaTX, is comprised by a conventional LNP-encapsulated RNA encoding a full-length prefusion stabilized S protein for SARS-CoV-2 [[162](#ref-Biu1CQeQ)]. As of August 11, 2022, 2 mRNA vaccines are available in 168 countries (Figure [3](#fig:mRNA-distrib)).

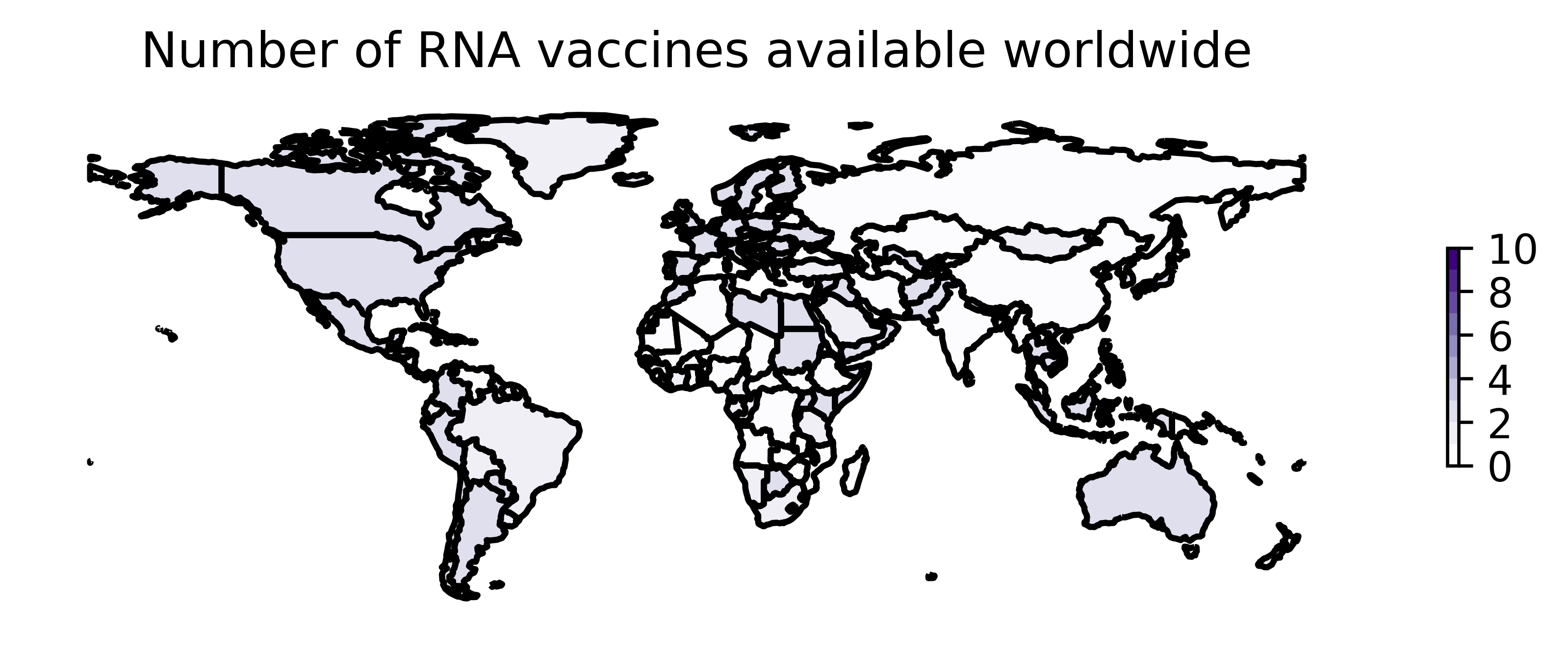


Figure 3: **Worldwide availability of vaccines developed using mRNA.** This figure reflects the number of vaccines based on mRNA technology that were available in each country as of August 11, 2022. These data are retrieved from Our World in Data [[128](#ref-sRy6js2o)] and plotted using geopandas [[129](#ref-iGEyNO42)]. See https://greenelab.github.io/covid19-review/ for the most recent version of this figure, which is updated daily.

**Trial Safety and Immunogenicity:** The VEs revealed by the Pfizer/BioNTech and Moderna clinical trials exceeded expectations. In a phase II/III 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 [[163](#ref-CWlYjjIV)]. The ModernaTX mRNA-1273 vaccine was the second mRNA vaccine to release phase III results, despite being the first mRNA vaccine to enter phase I clinical trials and publish interim results of their phase III 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 [[164](#ref-ZYxoabEm)]. Similar to BNT162b2, the mRNA-1273 vaccine was associated with mild-to-moderate AEs but with a low risk of serious AEs [[164](#ref-ZYxoabEm)]. In late 2020, both vaccines received approval from the FDA under an emergency use authorization [[165](#ref-cAaN4Te0),[166](#ref-13Ou1UUAd)], and these vaccines have been widely distributed, primarily in North America and the European Union [[167](#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.

**Real World Safety and Efficacy:** 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 [[168](#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. Concerns were also raised about a possible link between mRNA vaccination and myocarditis, especially in young men [[138](#ref-EqBIFx5T)].

## 0.10 Vaccines and Variants of Concern

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. COVID-19 vaccines have been challenged by the emergence of VOC. These VOC generally carry genetic 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 [[169](#ref-1B4h40dm5),[170](#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 [[171](#ref-x5yLFKk8),[172](#ref-19dwMfMGe),[173](#ref-63wnlBQD)], the greatest concern to date has been the Omicron variant (B.1.1.529), which was first identified in November 2021 [[170](#ref-yqFoGUHl),[174](#ref-k7L0WGEM)]. As of March 2022, the Omicron variant accounted for 95% of all infections sequenced in the United States [[175](#ref-1Bv67ENp2)] and was linked to an increased risk of SARS-CoV-2 reinfection [[169](#ref-1B4h40dm5)] and further infection of those who have been vaccinated with the mRNA vaccines [[176](#ref-lexoTbIa)].

In spite of vaccination programs, infection rates and hospitalization rates climbed in early 2022 in many Western countries including the United States [[177](#ref-19qv58Mv3),[178](#ref-TkFSco2t)]. Studies have reported claims of 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 [[179](#ref-gZ33CJWT)] and a reduced efficacy (70%) [[180](#ref-S6RHdOTJ)]. Estimates for the mRNA vaccines range from a 2-fold to over a 20-fold drop in neutralisation titers [[181](#ref-j172syOP)], hence the push for third and fourth doses of mRNA vaccines in many Western countries. A third mRNA vaccine dose does increase antibody titers, but these levels also wane with time [[182](#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 [[183](#ref-sNDCRMQ5)]. While antibody titers do correlate with protection [[184](#ref-J069om3D),[185](#ref-1AtNPSzpd),[186](#ref-QYbPf88B),[187](#ref-1HCZbWd9m),[188](#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.

The WHO continues to monitor the emergence of variants and their impact on vaccine efficacy [[189](#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 [[190](#ref-YlAWEwlx)]. To adapt, booster shots are now recommended in many places, and vaccines in the near future will likely account for multiple variants and strains of SARS-CoV-2 [[191](#ref-180UFKjJ2)].

## 0.11 Booster Doses

Due to waning neutralizing antibodies and viral evolution, boosters have emerged as an important strategy in retaining the benefits of vaccination over time. Homologous booster doses have been investigated for most vaccines. For example, over 14,000 adults were administered a booster (second) dose of the Janssen Ad26.COV2.S vaccine [[192](#ref-Cs2RaaCI)]. The booster dose was highly efficacious, with severe COVID-19 and hospitalization prevented almost completely in the vaccinated group. A booster dose was also found to improve immune response for Sputnik V vaccinees [[193](#ref-WtUhPusE)]. For the AstraZeneca vaccine, a different approach was taken. In the interest of distributing first doses as widely as possible, the effects of extending the time between the first and second doses was evaluated and [[194](#ref-17s40tqgW)].

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 showed that the additional immunization was 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 [[195](#ref-Jv71MaZb)]. Low efficacy against infection does not undermine the value of vaccination considering the vaccines are intended to prevent severe disease, hospitalization, and death rather than infection generally.

Many trials have also investigated heterologous boosting approaches. In particular, the mRNA vaccines are a popular choice following a primary series of a more traditional platform. In general, such approaches have been found to confer favorable immunogenicity relative to homologous boosters (e.g, [[196](#ref-L0dD93f8),[197](#ref-ybtjun8H),[198](#ref-H6vRjWQg),[199](#ref-15rMr9nh7),[200](#ref-cNs4cL36),[201](#ref-s1xmA2K6),[202](#ref-exu6jkTJ)] and many other studies). Due to remaining concerns about rare thromboembolic events, vaccinees who received AstraZeneca for their primary course are advised in some countries to seek a heterologous booster [[203](#ref-EzS3LTYM)], although such guidances are not supported by the evidence, which indicates that the first dose of AstraZeneca is most likely to be linked to these rare events [[204](#ref-kFl0x9VR)].

Although the vaccines developed based on the index strain remain highly effective at preventing severe illness and death, they serve much less utility at preventing illness broadly than they did early in the pandemic. Therefore, many manufacturers are exploring potential reformulations based on VOC that have emerged since the beginning of the pandemic. In June 2022, Moderna released data describing the effect of their bivalent mRNA booster, mRNA-1273.214, designed to protect against the Omicron variant [[205](#ref-OWsXXUTT)]. A 50 μg dose of mRNA-1273.214 was administered to 437 participants. One month later, the neutralizing geometric mean titer ratio was assessed against several variants of SARS-CoV-2, including Omicron. The immune response was higher against all variants assessed, including Omicron, than for boosting with the original formulation (mRNA-1273). Another formulation, mRNA-1273.211, developed based on the Beta variant, has been associated with durable protection as long as six months after dosing. These data are available through a press release and have not yet been published. Therefore, additional results may provide better insight into the VE of these formulations. Given the apparent need for boosters, interest has also emerged in whether updated formulations of SARS-CoV-2 vaccines can be administered along with annual flu vaccines to improve immunity to novel variants.

## 0.12 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 were initially so effective in preventing disease that they were also assumed to have an effect on the likelihood of transmission (e.g., venues requiring proof of vaccination). However, in light of the reduced efficacy in response to VOC, it is especially important to consider whether this assumption is supported by the available evidence.

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 II/III 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 [[206](#ref-ZU1ZF4SW)] (although viral shedding should not be conflated with contagiousness without further investigation [[8](#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 [[207](#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 [[208](#ref-34wAjHW5)] along with a systematic review finding a reduced probability of asymptomatic transmission [[209](#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 II/III trials, although the extent to which asymptomatic infection influenced these numbers was not investigated [[210](#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 [[211](#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) [[211](#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 (0.15%) and 19 developed asymptomatic COVID-19 (0.35%) [[212](#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.A. states from December 2020 to April 2021 reported a 40% reduction in viral load even with just a single dose of an mRNA vaccine [[168](#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 [[168](#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 [[213](#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 [[214](#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 [[214](#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 [[215](#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 [[216](#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 VOC, especially the Delta and Omicron variants, for which breakthrough infections are more common, the potential for vaccinated individuals to spread SARS-CoV-2 is not 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 [[214](#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.

## 0.13 Conclusions

COVID-19 has seen the coming-of-age of vaccine technologies that have been in development since the late 20th century but had never before received approvals. Vaccines that employ DNA and RNA eliminate all concerns about potential infection due to the vaccine components. The vaccines described above demonstrate the potential for these technologies to facilitate a quick response to an emerging pathogen. Additionally, their efficacy in trials far exceeded expectations, especially for RNA vaccines. These technologies hold significant potential to drive improvements in human health over the coming years.

Traditional vaccine technologies were built on the principle of using either a weakened version of the virus or a fragment of the virus. COVID-19 has highlighted the fact that in recent years, the field has undergone a paradigm shift towards reverse vaccinology. Reverse vaccinology emphasizes a hypothesis-free approach to vaccine development [[217](#ref-jU9YFYvB)]. This strategy was explored during development of a DNA vaccine against the Zika virus [[218](#ref-u0dESADU)]. Though 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 [[218](#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 [[39](#ref-BsrTDzJ2),[219](#ref-wPl93ATP)]. As a result, during the COVID-19 pandemic, these modular technologies have taken center stage in controlling a viral threat for the first time.

The large-scale emphasis on vaccine development has led to other advances. One example comes from ZyCoV-D, a DNA vaccine developed by the Indian company Cadila Healthcare. This vaccine uses a plasmid to deliver the expression-competent Spike protein and IgE signal peptides to the vaccinee [[220](#ref-1CCmltPec)]. During the phase I trial, vaccination with a needle versus a needle-free injection system was evaluated, and the vaccine can now be administered without a needle [[51](#ref-AfMvzFuk),[52](#ref-eIn1Qf3N)]. This highly portable design offers advantages over traditional vaccines [[220](#ref-1CCmltPec)], especially as the emergence of variants continues to challenge the efficacy of vaccines.

One of the downsides of this leap in vaccine technologies, however, is that they have largely been developed by wealthy countries, including countries in the European Union, the United States, the U.K., and Russia. As a result, they are also largely available to residents of wealthy countries, primarily in Europe and North America. Although the VE of DNA vaccines tends to be lower than that of mRNA vaccines [[221](#ref-YTceJugW)], they still provide excellent protection against severe illness and are much easier to distribute due to less complex demands for storage. Efforts such as COVAX that aim to expand access to vaccines developed by wealthy countries have not been as successful as hoped [[222](#ref-17V4Lh5uy)]. Fortunately, vaccine development programs using more established technologies have been undertaken in many middle income countries, and those vaccines have been more accessible globally [[1](#ref-S1SpDOhi)]. Additionally, efforts to develop new formulations of DNA vaccines in lower- and middle-income countries are increasingly being undertaken [[223](#ref-4eOROyon)].

The modular nature of nucleic acid-based vaccine platforms has opened a new frontier in responding to emerging viral illnesses. The RNA vaccines received an EUA in only a few months more than it took to identify the pathogen causing SARS in 2002. Given the variety of options available for preventing severe illness and death, it is possible that certain vaccines may be preferable for certain demographics (e.g., young women might choose an mRNA vaccine to entirely mitigate the very low risk of blood clots [[138](#ref-EqBIFx5T)]). However, this option is likely only available to people in high-income countries. In lower-income countries, access to vaccines broadly is a more critical issue. Different vaccines may confer advantages in different countries, and vaccine development in a variety of cultural contexts is therefore important [[224](#ref-hOkTKQ6z)]. Without widespread global availability of vaccines, SARS-CoV-2 will continue presenting a significant threat to people worldwide.

# 1 Additional Items

## 1.1 Competing Interests

| Author | Competing Interests | Last Reviewed |
| --- | --- | --- |
| Halie M. Rando | None | 2021-01-20 |
| Ronan Lordan | None | 2020-11-03 |
| Likhitha Kolla | None | 2020-11-16 |
| Elizabeth Sell | None | 2020-11-11 |
| Alexandra J. Lee | None | 2020-11-09 |
| Nils Wellhausen | None | 2020-11-03 |
| Amruta Naik | None | 2021-04-05 |
| COVID-19 Review Consortium | None | 2021-01-16 |
| Anthony Gitter | Filed a patent application with the Wisconsin Alumni Research Foundation related to classifying activated T cells | 2020-11-10 |
| Casey S. Greene | None | 2021-01-20 |

## 1.2 Author Contributions

| Author | Contributions |
| --- | --- |
| Halie M. Rando | Project Administration, Software, Writing - Original Draft, Writing - Review & Editing |
| Ronan Lordan | Project Administration, Writing - Original Draft, Writing - Review & Editing |
| Likhitha Kolla | Writing - Original Draft, Writing - Review & Editing |
| Elizabeth Sell | Writing - Review & Editing |
| Alexandra J. Lee | Writing - Review & Editing |
| Nils Wellhausen | Project Administration |
| Amruta Naik | Writing - Review & Editing |
| COVID-19 Review Consortium | Project Administration |
| Anthony Gitter | Writing - Review & Editing |
| Casey S. Greene | Conceptualization, Supervision, Writing - Original Draft |

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