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

This manuscript ([permalink](https://greenelab.github.io/covid19-review/v/c29ba0a665d80c3cb2795d5d2f54b85343ff23b2/)) was automatically generated from [greenelab/covid19-review@c29ba0a](https://github.com/greenelab/covid19-review/tree/c29ba0a665d80c3cb2795d5d2f54b85343ff23b2) on July 26, 2022. It is also available as a [PDF](https://greenelab.github.io/covid19-review/v/c29ba0a665d80c3cb2795d5d2f54b85343ff23b2/manuscript.pdf). It represents one section of a larger evolving review on SARS-CoV-2 and COVID-19 available at <https://greenelab.github.io/covid19-review/>

**This in progress manuscript is not intended for the general public.** This is a review paper that is authored by scientists for an audience of scientists to discuss research that is in progress. If you are interested in guidelines on testing, therapies, or other issues related to your health, you should not use this document. Instead, you should collect information from your local health department, the [CDC’s guidance](https://www.cdc.gov/coronavirus/2019-ncov/index.html), or your own government.

# Authors

* **Halie M. Rando** [0000-0001-7688-1770](https://orcid.org/0000-0001-7688-1770) [rando2](https://github.com/rando2) [tamefoxtime](https://twitter.com/tamefoxtime) Department of Systems Pharmacology and Translational Therapeutics, University of Pennsylvania, Philadelphia, Pennsylvania, United States of America; Department of Biochemistry and Molecular Genetics, University of Colorado School of Medicine, Aurora, Colorado, United States of America; Center for Health AI, University of Colorado School of Medicine, Aurora, Colorado, United States of America · Funded by the Gordon and Betty Moore Foundation (GBMF 4552); the National Human Genome Research Institute (R01 HG010067)
* **Ronan Lordan** [0000-0001-9668-3368](https://orcid.org/0000-0001-9668-3368) [RLordan](https://github.com/RLordan) [el\_ronan](https://twitter.com/el_ronan) Institute for Translational Medicine and Therapeutics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104-5158, USA; Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA; Department of Systems Pharmacology and Translational Therapeutics, Perelman School of Medicine, University of Pennsylvania; Philadelphia, PA 19104, USA
* **Likhitha Kolla** [0000-0002-1169-906X](https://orcid.org/0000-0002-1169-906X) [likhithakolla](https://github.com/likhithakolla) [lkolla2018](https://twitter.com/lkolla2018) Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, United States of America · Funded by NIH Medical Scientist Training Program T32 GM07170
* **Elizabeth Sell** [0000-0002-9658-1107](https://orcid.org/0000-0002-9658-1107) [esell17](https://github.com/esell17) Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, United States of America
* **Alexandra J. Lee** [0000-0002-0208-3730](https://orcid.org/0000-0002-0208-3730) [ajlee21](https://github.com/ajlee21) Department of Systems Pharmacology and Translational Therapeutics, University of Pennsylvania, Philadelphia, Pennsylvania, United States of America · Funded by the Gordon and Betty Moore Foundation (GBMF 4552)
* **Nils Wellhausen** [0000-0001-8955-7582](https://orcid.org/0000-0001-8955-7582) [nilswellhausen](https://github.com/nilswellhausen) Department of Systems Pharmacology and Translational Therapeutics, University of Pennsylvania, Philadelphia, Pennsylvania, United States of America
* **Amruta Naik** [0000-0003-0673-2643](https://orcid.org/0000-0003-0673-2643) [NAIKA86](https://github.com/NAIKA86) Children’s Hospital of Philadelphia, Philadelphia, PA, United States of America
* **COVID-19 Review Consortium**
* **Anthony Gitter** [0000-0002-5324-9833](https://orcid.org/0000-0002-5324-9833) [agitter](https://github.com/agitter) [anthonygitter](https://twitter.com/anthonygitter) Department of Biostatistics and Medical Informatics, University of Wisconsin-Madison, Madison, Wisconsin, United States of America; Morgridge Institute for Research, Madison, Wisconsin, United States of America · Funded by John W. and Jeanne M. Rowe Center for Research in Virology
* **Casey S. Greene** [0000-0001-8713-9213](https://orcid.org/0000-0001-8713-9213) [cgreene](https://github.com/cgreene) [GreeneScientist](https://twitter.com/GreeneScientist) Department of Systems Pharmacology and Translational Therapeutics, University of Pennsylvania, Philadelphia, Pennsylvania, United States of America; Childhood Cancer Data Lab, Alex’s Lemonade Stand Foundation, Philadelphia, Pennsylvania, United States of America; Department of Biochemistry and Molecular Genetics, University of Colorado School of Medicine, Aurora, Colorado, United States of America; Center for Health AI, University of Colorado School of Medicine, Aurora, Colorado, United States of America · Funded by the Gordon and Betty Moore Foundation (GBMF 4552); the National Human Genome Research Institute (R01 HG010067)

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

Authors with similar contributions are ordered alphabetically.

## 0.1 Abstract

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 July 24, 2022, SARS-CoV-2 has infected over 570,190,176 and taken the lives of 6,384,335 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. Previously only theoretical technologies have taken a leading role in the management of 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. With at least 570,190,176 cases and 6,384,335 deaths, the impact of the virus on the human species has been significant. 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 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 the companion manuscript, 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 of a antigen can be introduced, eliminating most of the risks of vaccination. 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), 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 [[1](#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 [[2](#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 [[2](#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 [[3](#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 [[4](#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 [[5](#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 reached the level of pandemic (see visualization in [[6](#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 [[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, 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/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 [[8](#ref-fQvzeptv),[9](#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 [[9](#ref-1GA95MF2m)], and by September 2020, there were over 180 vaccine candidates against SARS-CoV-2 in development [[10](#ref-dqpEe5Lz)]. As of July 24, 2022, 40 SARS-CoV-2 vaccines have been approved world wide and 28 are being administered throughout the world, with 12.0 billion doses administered across 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 [[11](#ref-vlGP3RAU)] (Figure ??). This genomic information allowed for an early identification of the sequence of the spike (S) protein (Figure ??), which is the antigen and induces an immune response [[12](#ref-Vnbw9o3T),[13](#ref-13wCBLnnu)].

During the development process, one measure used to assess whether a vaccine candidate is likely to provide protection is serum neutralizing activity [[14](#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. 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 (Figure ??), 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 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 [[15](#ref-R7Xdh5nH)], and the release of energy during membrane fusion drives this process forward following destabilization [[16](#ref-17DSmRo9H),[17](#ref-3uddYea8)]. Due to the significant conformational changes that occur during membrane fusion [[18](#ref-qcVbT0w4),[19](#ref-hIc3bKWe),[20](#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 [[21](#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 [[21](#ref-oghHqZDt),[22](#ref-13wWdgODZ),[23](#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 [[24](#ref-lvq9hGmj)]. The immune response to the spike protein when it is stabilized in this conformation is improved over other S structures [[25](#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 [[26](#ref-13bVbfc5h),[27](#ref-122h6fIxE),[28](#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 [[29](#ref-17qiILENK)]. To date, the most significant variants of concern identified are alpha (2020), beta (2020), gamma (2020), delta (2021) and omicron (2021). The efficacy of vaccines in the context of these variants is discussed where information is available.

## 0.7 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 [[30](#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 [[31](#ref-MCZBJ5sF),[32](#ref-fw8IwtHq)]. In this way, the genomic revolution catalyzed a fundamental shift in the development of vaccines. Such technologies hold the potential to 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 [[33](#ref-kqerKJKY)].

Nucleic-acid based approaches share an underlying principle: a vector that delivers the information needed to produce an antigen can trigger an immune response 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* [[34](#ref-YY3x3bBV)]. Studies also demonstrated that model organisms could be induced to construct antigens that would trigger an immune response [[35](#ref-U9ZIZWkB),[36](#ref-pWMIo6pD),[37](#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 [[38](#ref-BsrTDzJ2)]. Delivering a nucleic acid sequence to host cells allows the host to synthesize an antigen without exposure to a viral threat [[38](#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 [[38](#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 [[38](#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 [[32](#ref-fw8IwtHq)], and pathogens of interest are then expressed *in vitro* and tested in animal models to determine their immunogenicity [[32](#ref-fw8IwtHq)]. By inducing the host to express the antigen, such vaccines can activate immune pathways via both MHC I and MHC II [[39](#ref-fwumPoq1)] instead of MHC II alone as with prior technologies [[37](#ref-uPszIvSj)]. This dual presentation means that both humoral and cellular immunity are activated [[38](#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 [[38](#ref-BsrTDzJ2),[40](#ref-29LxSWHB)].

## 0.8 DNA Vaccine Platforms

DNA vaccine technologies have developed slowly over the past thirty years. Early attempts revealed issues with low immunogenicity [[35](#ref-U9ZIZWkB),[37](#ref-uPszIvSj),[37](#ref-uPszIvSj),[41](#ref-12jFcMeQY)]. Additionally, initial skepticism about the approach suggested that DNA vaccines might bind to the host genome or induce autoimmune disease [[38](#ref-BsrTDzJ2),[39](#ref-fwumPoq1)], but pre-clinical and clinical studies have consistently disproved this hypothesis and indicated DNA vaccines to be safe [[41](#ref-12jFcMeQY)]. These safety concerns 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 [[38](#ref-BsrTDzJ2)]. While this issue was resolved through strategic vector design [[42](#ref-Wjtx0VXu),[43](#ref-5fcD0JWR)], the immunogenicity of these vaccines did not reach expectations [[38](#ref-BsrTDzJ2)].

Several developments during the 2010s led to greater efficacy of DNA vaccines [[38](#ref-BsrTDzJ2)]. However, no DNA vaccines had been approved for use in humans prior to the COVID-19 pandemic [[41](#ref-12jFcMeQY),[44](#ref-yriARFOF)]. As of July 25, 2022, XX vaccines have been approved worldwide (Table ??). 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 [[45](#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 [[46](#ref-XnrBoKVk)]. Plasmids can also be designed to act as adjuvants by encoding molecules that supplement the immune response, such as immune stimulant molecules [[39](#ref-fwumPoq1)]. The DNA itself may also stimulate the innate immune response [[37](#ref-uPszIvSj),[43](#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 [[38](#ref-BsrTDzJ2)]. The vectors are edited to remove extra sequences [[43](#ref-5fcD0JWR)]. Advances such as this on the manufacturing side have improved the safety and throughput of this platform [[43](#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 [[38](#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 [[38](#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 [[38](#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 [[50](#ref-AfMvzFuk),[51](#ref-eIn1Qf3N)].

Similarly, another plasmid-vectored DNA vaccine, INO-4800 [[52](#ref-xuzLfS0y)], was developed by Inovio Pharmaceuticals Technology that uses electroportion 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 [[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 vaccines therefore represent 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 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 [[56](#ref-OYnqjMlC)]. The phase 2/3 trials are ongoing in several countries, including the United States, Mexico, India, and Colombia [[57](#ref-pxEE3VEQ),[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:** The efficacy of ZyCoV-D is estimated at 66.6% [[61](#ref-3xlXzOoW)]. Because phase 3 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 VOC. They assessed neutralization of several VOC relative to the index strain [[62](#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) [[62](#ref-mbBuH8XY)]. These findings are in line with the shifts in efficacy reported for other vaccines [[30](#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 [[63](#ref-CSlbNoGU)]. Administration of a booster dose induced a significant increase of titers relative to their pre-booster levels [[63](#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 [[64](#ref-ysgD4Dcf)]. Known as INO-4802, this vaccine was designed to express a pan-Spike immunogen [[65](#ref-Aynz3sBj)]. Booster studies in rodents [[66](#ref-12zreC1Tk)] and non-human primates [[65](#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 [[65](#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 using a second virus as a vector [[67](#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 [[68](#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 [[38](#ref-BsrTDzJ2)].

One of the early viral vectors explored was adenovirus, with serotype 5 (Ad5) being particularly effective [[38](#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 [[38](#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 [[38](#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 [[38](#ref-BsrTDzJ2),[79](#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 [[80](#ref-9g5tmszW)]. Additionally, several phase 1 and phase 2 clinical trials for other vaccines are ongoing [[67](#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 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 [[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 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 [[94](#ref-1037p4Gvs)]. In a phase 1 trial, 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)]. In a phase 1/2 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 [[95](#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 [[96](#ref-sRAZYY9C)], as some individuals may possess immunity to Ad5 [[97](#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’s “Operation Warp Speed” [[98](#ref-D3Px25HN),[99](#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 [[25](#ref-10UC562ga),[100](#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 [[101](#ref-gOOBv1MD)]. JNJ-78436735 was selected from among a number of initial candidate designs [[25](#ref-10UC562ga)] and tested *in vivo* in Syrian golden hamsters and Rhesus macaques to assess safety and immunogenicity [[25](#ref-10UC562ga),[101](#ref-gOOBv1MD),[102](#ref-HmMIiIv2),[103](#ref-EpOXYGt4)]. The JNJ-78436735 candidate was selected for its favorable immunogenicity profile and ease of manufacturability [[25](#ref-10UC562ga),[101](#ref-gOOBv1MD),[102](#ref-HmMIiIv2),[103](#ref-EpOXYGt4)] and was found to confer protection against SARS-CoV-2 in macaques even after six months [[104](#ref-HGVDPMLm)]. The one- versus two-dose regimen was then tested in volunteers through a phase 1/2a trial [[100](#ref-pWf2T8J8),[105](#ref-69GoEX0X)]. A major difference between this vaccine and the other two in this category is that here, 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 3 trial were released detailing randomized control trials conducted in the United Kingdom (U.K.), Brazil, and South Africa between April and November 2020 [[12](#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 3 trial indicated an overall vaccine efficacy of 91.6% for symptomatic COVID-19 [[106](#ref-gLAIyAHm)]. As for Janssen, in February 2021, the FDA issued an EUA based on interim results from the phase 3 trial [[107](#ref-iWMHpTBJ),[108](#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 [[109](#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 [[109](#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 [[110](#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 [[111](#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 [[111](#ref-JSzDvnk6),[112](#ref-Yzz3rwqk)]. Interim results of the phase III trial weren’t published until the following February [[106](#ref-gLAIyAHm)]. 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 [[110](#ref-3KMxmQhV),[113](#ref-15DiM98Ae),[114](#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 [[110](#ref-3KMxmQhV)]. Almost a month later, the phase I/II trial data was published [[115](#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 [[106](#ref-gLAIyAHm)].

AstraZeneca’s clinical trial also faced criticism. The trial was paused in September 2020 following a severe adverse event in one participant [[116](#ref-vwhmuwto)]. It was restarted soon after [[117](#ref-Fz6kXAHy)], but it seems that the recent pause was not mentioned to the FDA during a call the morning before the story broke [[118](#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 [[119](#ref-4mDUvRId)]. Combining the data then led to confusion surrounding the vaccine’s efficacy, 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 [[12](#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 [[120](#ref-SUGCFKUo)]. Therefore, this error may serendipitously improve efficacy of vaccine-vectored vaccines broadly.

**Real-World Safety and Efficacy:** As of July 24, 2022, 3 viral-vectored vaccines are being distributed in 195 countries (Figure [1](#fig:nrvv-distrib)). ChAdOx1 nCoV-19 was first approved for emergency use on December 30, 2020 in the U.K. [[121](#ref-1A7PjhDDR)]. As early as January 2021, Sputnik V had been administered to 1.5 million Russians [[122](#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 [[123](#ref-16LczMwFO),[124](#ref-Z0V7NK7Y),[125](#ref-16GYKbrOq)], with the Czech Republic and Austria also having expressed interest in its procurement [[126](#ref-125VEHWS7)].

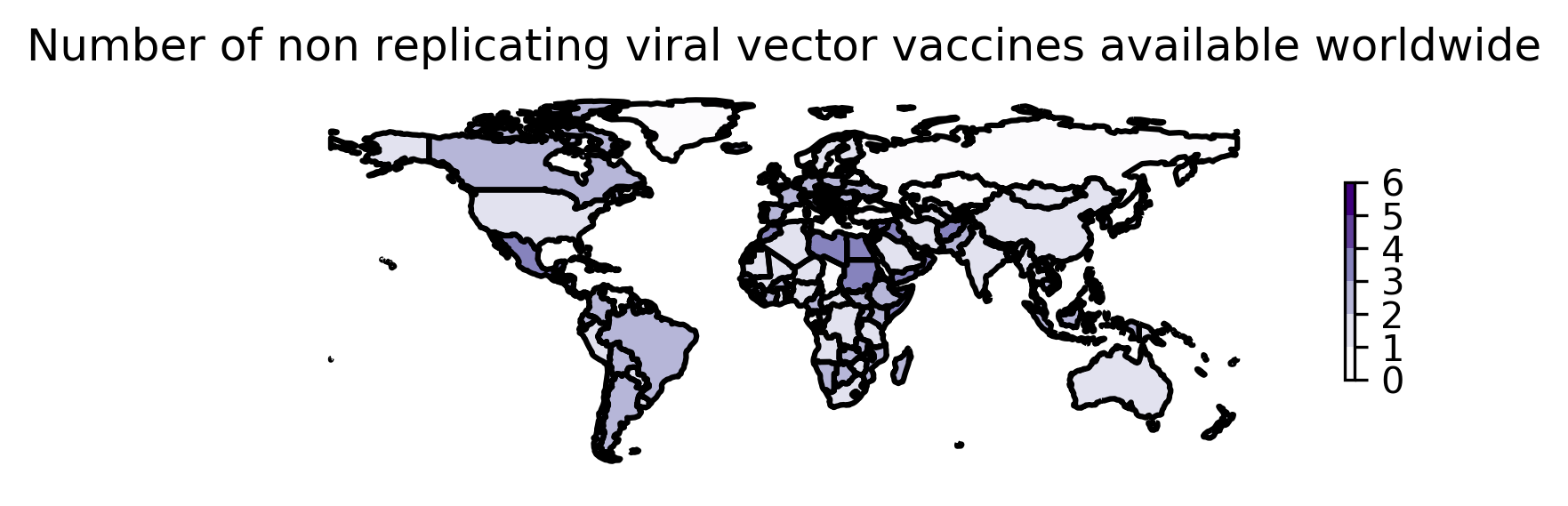


Figure 1: **Worldwide availability of vaccines developed using non-replicating viral vectors.** This figure reflects the number of vaccines using non-replicating viral vectors that were available in each country as of July 24, 2022. These data are retrieved from Our World in Data [[127](#ref-sRy6js2o)] and plotted using geopandas. 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 [[128](#ref-5gqQwOi6)]. In March 2021, administration of the vaccine was paused in several European countries while a possible link to thrombotic events was investigated [[129](#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 [[130](#ref-xSBGseR)]. The following month, the United States paused administration of the Janssen vaccine for ten days due to 15 similar AEs [[131](#ref-TtPVfMOL),[132](#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 [[133](#ref-iRvYqPq6),[134](#ref-MnBdD0Mr),[135](#ref-2uAR3HBq),[136](#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 [[137](#ref-tTpW7jvQ)]. Estimates of the incidence in other western countries have also been low [[138](#ref-rWaWz2Yg)]. In the US, thromboembolic events following the Janssen vaccine have also been very rare [[134](#ref-MnBdD0Mr)]. Subsequently, a potential mechanism was identified: the adenovirus vector binding to platelet factor 4 (PF4) [[139](#ref-z5vyJuGl),[140](#ref-XwlVcLVP)]. Because this adverse event is so rare, the risk is likely still outweighed by the risks associated with contracting COVID-19 [[141](#ref-itL8KsXg)]] which is also associated with thrombotic events) [[132](#ref-1F1ma0vMT),[142](#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 [[136](#ref-EqBIFx5T)].

## 0.9 RNA Vaccines

Table 2: Approved RNA vaccines [[45](#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 [[143](#ref-D7ou3S22),[144](#ref-2YZ70C2y)]. mRNA contains the minimum information needed to create a protein [[144](#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 [[144](#ref-2YZ70C2y),[145](#ref-ENBWnhAh)].

The mRNA technology is transcribed *in vitro* and delivered to cells via lipid nanoparticles (LNP) [[146](#ref-HCImhzy8)]. They are recognized by ribosomes *in vivo* and then translated and modified into functional proteins [[147](#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 [[147](#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 [[148](#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 [[147](#ref-K0Ltu31S),[149](#ref-pRoqjur8)].

There are three types of RNA vaccines: non-replicating, *in vivo* self-replicating, and *in vitro* dendritic cell non-replicating [[150](#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 [[147](#ref-K0Ltu31S),[149](#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 [[147](#ref-K0Ltu31S)]. Self-replicating vaccines produce more viral antigens over a longer period of time, thereby evoking a more robust immune response [[150](#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 [[151](#ref-3LMMW7F0)]. These cells are isolated from the patient, grown and transfected *ex vivo*, and reintroduced to the patient [[145](#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 [[152](#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 [[147](#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 [[153](#ref-3EUiWZdN)]. Preclinical data previously identified effective antibody generation against full-length FPLC-purified influenza hemagglutinin stalk-encoding mRNA in mice, rabbits, and ferrets [[154](#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 [[149](#ref-pRoqjur8)]. Positively charged bilayer LNPs carrying the mRNA attract negatively charged cell membranes, endocytose into the cytoplasm [[148](#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 [[148](#ref-zNKWlCwE),[155](#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 [[33](#ref-kqerKJKY),[156](#ref-17lluDFcc)]. As of the 2010s, mRNA was still considered a promising technology for future advances in vaccine development [[144](#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 [[145](#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 [[157](#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 [[158](#ref-1CsCQi9wT),[159](#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 [[160](#ref-Biu1CQeQ)]. As of July 24, 2022, 2 mRNA vaccines are available in 168 countries (Figure [2](#fig:mRNA-distrib)).

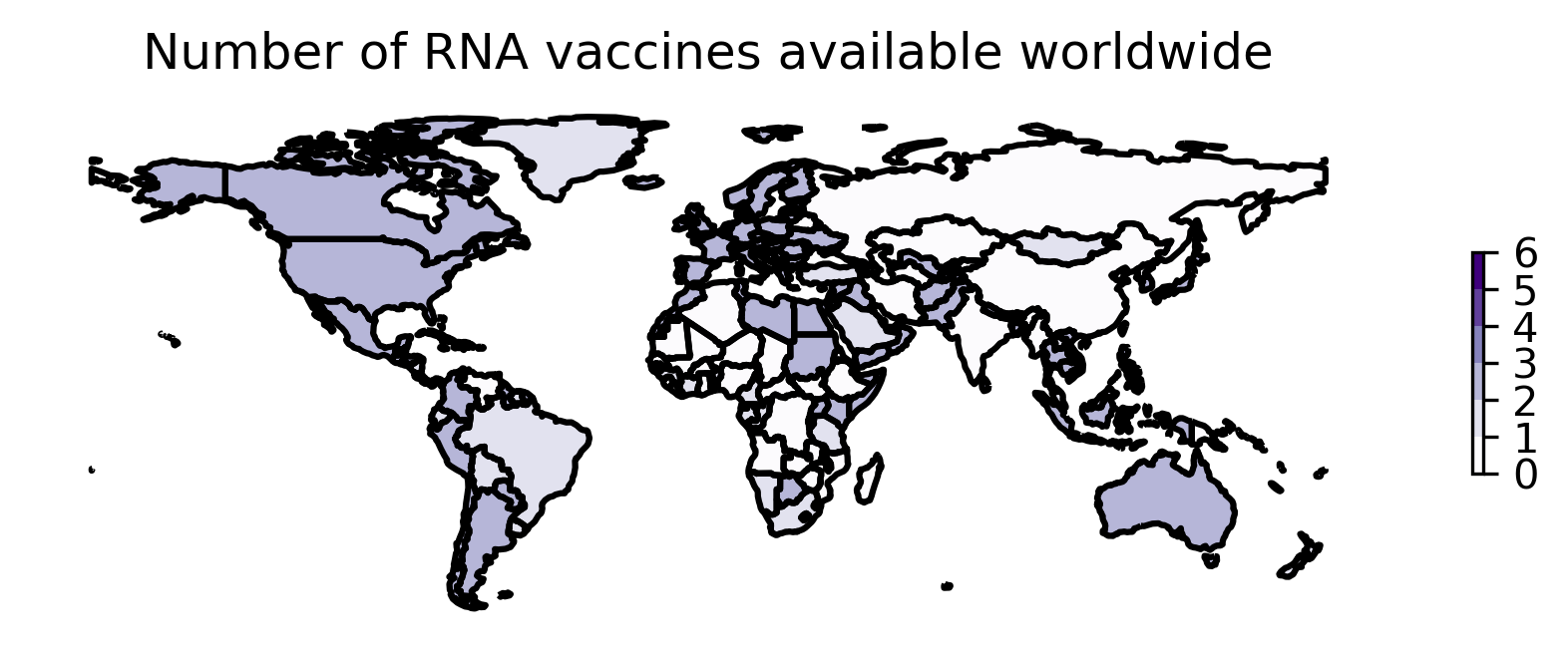


Figure 2: **Worldwide availability of vaccines developed using mRNA.** This figure reflects the number of vaccines based on mRNA technology that were available in each country as of July 24, 2022. These data are retrieved from Our World in Data [[127](#ref-sRy6js2o)] and plotted using geopandas. See https://greenelab.github.io/covid19-review/ for the most recent version of this figure, which is updated daily.

**Trial Safety and Immunogenicity:** The VEs revealed by the Pfizer/BioNTech and Moderna clinical trials exceeded expectations. 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 [[161](#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 [[162](#ref-ZYxoabEm)]. Similar to BNT162b2, the mRNA-1273 vaccine was associated with mild-to-moderate AEs but with a low risk of serious AEs [[162](#ref-ZYxoabEm)]. In late 2020, both vaccines received approval from the FDA under an emergency use authorization [[163](#ref-cAaN4Te0),[164](#ref-13Ou1UUAd)], and these vaccines have been widely distributed, primarily in North America and the European Union [[165](#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 [[166](#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 [[136](#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 variants of concern (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 [[167](#ref-1B4h40dm5),[168](#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 [[169](#ref-x5yLFKk8),[170](#ref-19dwMfMGe),[171](#ref-63wnlBQD)], the greatest concern to date has been the Omicron variant (B.1.1.529), which was first identified in November 2021 [[168](#ref-yqFoGUHl),[172](#ref-k7L0WGEM)]. As of March 2022, the Omicron variant accounts for 95% of all infections sequenced in the United States [[173](#ref-1Bv67ENp2)] and has been linked to an increased risk of SARS-CoV-2 reinfection [[167](#ref-1B4h40dm5)] and further infection of those who have been vaccinated with the mRNA vaccines [[174](#ref-lexoTbIa)].

In spite of vaccination programs, infection rates and hospitalization rates climbed in early 2022 in many Western countries including the United States [[175](#ref-19qv58Mv3),[176](#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 [[177](#ref-gZ33CJWT)] and a reduced efficacy (70%) [[178](#ref-S6RHdOTJ)]. Estimates for the mRNA vaccines range from a 2-fold to over a 20-fold drop in neutralisation titers [[179](#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 [[180](#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 [[181](#ref-sNDCRMQ5)]. While antibody titers do correlate with protection [[182](#ref-J069om3D),[183](#ref-1AtNPSzpd),[184](#ref-QYbPf88B),[185](#ref-1HCZbWd9m),[186](#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 [[187](#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 [[188](#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 [[189](#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 [[190](#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 [[191](#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 [[192](#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 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 [[193](#ref-Jv71MaZb)]. Low efficacy against infection does not undermine the value of vaccination considering the vaccines are intended to prevent against 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, [[194](#ref-L0dD93f8),[195](#ref-ybtjun8H),[196](#ref-H6vRjWQg),[197](#ref-15rMr9nh7),[198](#ref-cNs4cL36),[199](#ref-s1xmA2K6),[200](#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 [[201](#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 [[202](#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 in the years 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 [[203](#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 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 [[204](#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 [[205](#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 [[206](#ref-34wAjHW5)] along with a systematic review finding a reduced probability of asymptomatic transmission [[207](#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 [[208](#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 [[209](#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) [[209](#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%) [[210](#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 [[166](#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 [[166](#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 [[211](#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 [[212](#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 [[212](#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 [[213](#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 [[214](#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 and omicron variants, 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 [[212](#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. The vaccines described above demonstrate the potential for this technology 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 [[215](#ref-jU9YFYvB)]. This strategy was explored during development of a DNA vaccine against the Zika virus [[216](#ref-u0dESADU)]. Though the disease was controlled before the vaccine became available [[2](#ref-HyYY2agc)], the response demonstrated the potential for modular technologies to facilitate a response to emerging viral threats [[216](#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 [[38](#ref-BsrTDzJ2),[217](#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 vacinee [[218](#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 [[218](#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. The DNA vaccines, while their VE tends to be lower than that of mRNA vaccines (even, for example, in a head-to-head comparison [[219](#ref-YTceJugW)]), 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 [[220](#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 [[30](#ref-S1SpDOhi)]. Additionally, efforts to develop new formulations of DNA vaccines in lower and middle income countries are increasingly being undertaken [[221](#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 had 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 [[136](#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 [[222](#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 |

## 1.3 Acknowledgements

We thank Nick DeVito for assistance with the Evidence-Based Medicine Data Lab COVID-19 TrialsTracker data. We thank Yael Evelyn Marshall who contributed writing (original draft) as well as reviewing and editing of pieces of the text but who did not formally approve the manuscript, as well as Ronnie Russell, who contributed text to and helped develop the structure of the manuscript early in the writing process and Matthias Fax who helped with writing and editing text related to diagnostics. We are also very grateful to James Fraser for suggestions about successes and limitations in the area of computational screening for drug repurposing. We are grateful to the following contributors for reviewing pieces of the text: Nadia Danilova, James Eberwine and Ipsita Krishnan.

## 1.4 References

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

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

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

4. **Ebola vaccine: Little and late** Jon Cohen *Science* (2014-09-19) <https://doi.org/gm2qkd> DOI: [10.1126/science.345.6203.1441](https://doi.org/10.1126/science.345.6203.1441) · PMID: [25237082](https://www.ncbi.nlm.nih.gov/pubmed/25237082)

5. **Clinical development of a recombinant Ebola vaccine in the midst of an unprecedented epidemic** Beth-Ann G Coller, Jeffrey Blue, Rituparna Das, Sheri Dubey, Lynn Finelli, Swati Gupta, Frans Helmond, Rebecca J Grant-Klein, Kenneth Liu, Jakub Simon, … Thomas P Monath *Vaccine* (2017-08) <https://doi.org/gbw3rt> DOI: [10.1016/j.vaccine.2017.05.097](https://doi.org/10.1016/j.vaccine.2017.05.097) · PMID: [28647166](https://www.ncbi.nlm.nih.gov/pubmed/28647166)

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

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

8. **Our Story** Moderna <https://www.modernatx.com/en-US/about-us/our-story?slug=about-us%2Four-story>

9. **The COVID-19 vaccine development landscape** Tung Thanh Le, Zacharias Andreadakis, Arun Kumar, Raúl Gómez Román, Stig Tollefsen, Melanie Saville, Stephen Mayhew *Nature Reviews Drug Discovery* (2020-04-09) <https://doi.org/ggrnbr> DOI: [10.1038/d41573-020-00073-5](https://doi.org/10.1038/d41573-020-00073-5) · PMID: [32273591](https://www.ncbi.nlm.nih.gov/pubmed/32273591)

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

11. **Novel Coronavirus – China** <https://www.who.int/emergencies/disease-outbreak-news/item/2020-DON233>

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

30. **Application of Traditional Vaccine Development Strategies to SARS-CoV-2** COVID-19 Review Consortium *Manubot* (2022-06-21) <https://greenelab.github.io/covid19-review/v/d9d90fd7e88ef547fb4cbed0ef73baef5fee7fb5/#vaccine-development-strategies-for-sars-cov-2>

31. **Towards Vaccine 3.0: new era opened in vaccine research and industry** Joon Haeng Rhee *Clinical and Experimental Vaccine Research* (2014) <https://doi.org/gmqmg4> DOI: [10.7774/cevr.2014.3.1.1](https://doi.org/10.7774/cevr.2014.3.1.1) · PMID: [24427757](https://www.ncbi.nlm.nih.gov/pubmed/24427757) · PMCID: [PMC3890443](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3890443)

32. **Developing vaccines in the era of genomics: a decade of reverse vaccinology** KL Seib, X Zhao, R Rappuoli *Clinical Microbiology and Infection* (2012-10) <https://doi.org/gkbn9x> DOI: [10.1111/j.1469-0691.2012.03939.x](https://doi.org/10.1111/j.1469-0691.2012.03939.x) · PMID: [22882709](https://www.ncbi.nlm.nih.gov/pubmed/22882709)

33. **A Comparison of Plasmid DNA and mRNA as Vaccine Technologies** Liu *Vaccines* (2019-04-24) <https://doi.org/ggwd7r> DOI: [10.3390/vaccines7020037](https://doi.org/10.3390/vaccines7020037) · PMID: [31022829](https://www.ncbi.nlm.nih.gov/pubmed/31022829) · PMCID: [PMC6631684](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6631684)

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

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

36. **New Vaccine Technologies** Ronald W Ellis *JAMA: The Journal of the American Medical Association* (1994-03-23) <https://doi.org/b8gn86> DOI: [10.1001/jama.1994.03510360055036](https://doi.org/10.1001/jama.1994.03510360055036)

37. **DNA vaccines: a review** MA Liu *Journal of Internal Medicine* (2003-04) <https://doi.org/c9z766> DOI: [10.1046/j.1365-2796.2003.01140.x](https://doi.org/10.1046/j.1365-2796.2003.01140.x) · PMID: [12653868](https://www.ncbi.nlm.nih.gov/pubmed/12653868)

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

39. **Plasmid DNA vaccines: where are we now?** F Ghaffarifar *Drugs of Today* (2018) <https://doi.org/gdsqgg> DOI: [10.1358/dot.2018.54.5.2807864](https://doi.org/10.1358/dot.2018.54.5.2807864) · PMID: [29911696](https://www.ncbi.nlm.nih.gov/pubmed/29911696)

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

41. **DNA Vaccines—How Far From Clinical Use?** Dominika Hobernik, Matthias Bros *International Journal of Molecular Sciences* (2018-11-15) <https://doi.org/gmqmg3> DOI: [10.3390/ijms19113605](https://doi.org/10.3390/ijms19113605) · PMID: [30445702](https://www.ncbi.nlm.nih.gov/pubmed/30445702) · PMCID: [PMC6274812](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6274812)

42. **Ensuring safety of DNA vaccines** Jacob Glenting, Stephen Wessels *Microbial Cell Factories* (2005-09-06) <https://doi.org/b4rbhw> DOI: [10.1186/1475-2859-4-26](https://doi.org/10.1186/1475-2859-4-26) · PMID: [16144545](https://www.ncbi.nlm.nih.gov/pubmed/16144545) · PMCID: [PMC1215512](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1215512)

43. **Vector Design for Improved DNA Vaccine Efficacy, Safety and Production** James Williams *Vaccines* (2013-06-25) <https://doi.org/gcfsx2> DOI: [10.3390/vaccines1030225](https://doi.org/10.3390/vaccines1030225) · PMID: [26344110](https://www.ncbi.nlm.nih.gov/pubmed/26344110) · PMCID: [PMC4494225](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4494225)

44. **Engineered Nanodelivery Systems to Improve DNA Vaccine Technologies** Michael Lim, Abu Zayed Md Badruddoza, Jannatul Firdous, Mohammad Azad, Adnan Mannan, Taslim Ahmed Al-Hilal, Chong-Su Cho, Mohammad Ariful Islam *Pharmaceutics* (2020-01-01) <https://doi.org/ghwmkd> DOI: [10.3390/pharmaceutics12010030](https://doi.org/10.3390/pharmaceutics12010030) · PMID: [31906277](https://www.ncbi.nlm.nih.gov/pubmed/31906277) · PMCID: [PMC7022884](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7022884)

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

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

47. **Human Clinical Trials of Plasmid DNA Vaccines** Margaret A Liu, Jeffrey B Ulmer *Advances in Genetics* (2005) <https://doi.org/bvm6vh> DOI: [10.1016/s0065-2660(05)55002-8](https://doi.org/10.1016/s0065-2660(05)55002-8)

48. **Induction of antigen-specific CD8+ T cells, T helper cells, and protective levels of antibody in humans by particle-mediated administration of a hepatitis B virus DNA vaccine** Michael J Roy, Mary S Wu, Lori James Barr, James T Fuller, Lynda G Tussey, Sue Speller, Jerilyn Culp, Joseph K Burkholder, William F Swain, Russell M Dixon, … Deborah Heydenburg Fuller *Vaccine* (2000-11) <https://doi.org/c9ntfp> DOI: [10.1016/s0264-410x(00)00302-9](https://doi.org/10.1016/s0264-410x(00)00302-9)

49. **Plasmid-Based DNA Vaccines** Leonardo A. Gómez, Angel A. Oñate *Plasmid* (2019-06-19) <https://doi.org/gp4rrk> DOI: [10.5772/intechopen.76754](https://doi.org/10.5772/intechopen.76754)

50. **India’s cost-effective COVID-19 vaccine development initiatives** Chiranjib Chakraborty, Govindasamy Agoramoorthy *Vaccine* (2020-11) <https://doi.org/gp432n> DOI: [10.1016/j.vaccine.2020.10.056](https://doi.org/10.1016/j.vaccine.2020.10.056) · PMID: [33129610](https://www.ncbi.nlm.nih.gov/pubmed/33129610) · PMCID: [PMC7574682](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7574682)

51. **India’s DNA COVID vaccine is a world first – more are coming** Smriti Mallapaty *Nature* (2021-09-02) <https://doi.org/gp432q> DOI: [10.1038/d41586-021-02385-x](https://doi.org/10.1038/d41586-021-02385-x) · PMID: [34475553](https://www.ncbi.nlm.nih.gov/pubmed/34475553)

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

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

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

55. **Safety and immunogenicity of INO-4800 DNA vaccine against SARS-CoV-2: A preliminary report of an open-label, Phase 1 clinical trial** Pablo Tebas, ShuPing Yang, Jean D Boyer, Emma L Reuschel, Ami Patel, Aaron Christensen-Quick, Viviane M Andrade, Matthew P Morrow, Kimberly Kraynyak, Joseph Agnes, … Laurent M Humeau *EClinicalMedicine* (2021-01) <https://doi.org/gh6xbh> DOI: [10.1016/j.eclinm.2020.100689](https://doi.org/10.1016/j.eclinm.2020.100689) · PMID: [33392485](https://www.ncbi.nlm.nih.gov/pubmed/33392485) · PMCID: [PMC7759123](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7759123)

56. **Safety and immunogenicity of INO-4800 DNA vaccine against SARS-CoV-2: a preliminary report of a randomized, blinded, placebo-controlled, Phase 2 clinical trial in adults at high risk of viral exposure** Mammen P Mammen Jr., Pablo Tebas, Joseph Agnes, Mary Giffear, Kimberly A Kraynyak, Elliott Blackwood, Dinah Amante, Emma L Reuschel, Mansi Purwar, Aaron Christensen-Quick, … Laurent M Humeau *Cold Spring Harbor Laboratory* (2021-05-07) <https://doi.org/gp432t> DOI: [10.1101/2021.05.07.21256652](https://doi.org/10.1101/2021.05.07.21256652)

57. **INOVIO Receives U.S. FDA Authorization to Proceed with INNOVATE Phase 3 Segment for its COVID-19 Vaccine Candidate, INO-4800, in the U.S.** <https://ir.inovio.com/news-releases/news-releases-details/2021/INOVIO-Receives-U.S.-FDA-Authorization-to-Proceed-with-INNOVATE-Phase-3-Segment-for-its-COVID-19-Vaccine-Candidate-INO-4800-in-the-U.S/default.aspx>

58. **INOVIO Further Expands INNOVATE Phase 3 Trial for COVID-19 DNA Vaccine Candidate INO-4800 With Regulatory Authorization from India** <https://ir.inovio.com/news-releases/news-releases-details/2021/INOVIO-Further-Expands-INNOVATE-Phase-3-Trial-for-COVID-19-DNA-Vaccine-Candidate-INO-4800-With-Regulatory-Authorization-from-India/default.aspx>

59. **INOVIO Expands INNOVATE Phase 3 for INO-4800, its DNA Vaccine Candidate for COVID-19, to include Colombia following Regulatory Authorization** <https://ir.inovio.com/news-releases/news-releases-details/2021/INOVIO-Expands-INNOVATE-Phase-3-for-INO-4800-its-DNA-Vaccine-Candidate-for-COVID-19-to-include-Colombia-following-Regulatory-Authorization/default.aspx>

60. **INOVIO Receives Regulatory Authorization to Conduct Phase 3 Efficacy Trial of its COVID-19 DNA Vaccine Candidate, INO-4800, in Mexico** <https://ir.inovio.com/news-releases/news-releases-details/2021/INOVIO-Receives-Regulatory-Authorization-to-Conduct-Phase-3-Efficacy-Trial-of-its-COVID-19-DNA-Vaccine-Candidate-INO-4800-in-Mexico/default.aspx>

61. **Efficacy, safety, and immunogenicity of the DNA SARS-CoV-2 vaccine (ZyCoV-D): the interim efficacy results of a phase 3, randomised, double-blind, placebo-controlled study in India** Akash Khobragade, Suresh Bhate, Vijendra Ramaiah, Shrikant Deshpande, Krishna Giri, Himanshu Phophle, Pravin Supe, Inderjeet Godara, Ramesh Revanna, Rajnish Nagarkar, … Parshottam Koradia *The Lancet* (2022-04) <https://doi.org/hvqb> DOI: [10.1016/s0140-6736(22)00151-9](https://doi.org/10.1016/s0140-6736(22)00151-9) · PMID: [35367003](https://www.ncbi.nlm.nih.gov/pubmed/35367003) · PMCID: [PMC8970574](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8970574)

62. **INO-4800 DNA vaccine induces neutralizing antibodies and T cell activity against global SARS-CoV-2 variants** Viviane M Andrade, Aaron Christensen-Quick, Joseph Agnes, Jared Tur, Charles Reed, Richa Kalia, Idania Marrero, Dustin Elwood, Katherine Schultheis, Mansi Purwar, … Kate E Broderick *npj Vaccines* (2021-10-14) <https://doi.org/gns5ff> DOI: [10.1038/s41541-021-00384-7](https://doi.org/10.1038/s41541-021-00384-7) · PMID: [34650089](https://www.ncbi.nlm.nih.gov/pubmed/34650089) · PMCID: [PMC8516974](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8516974)

63. **SARS-CoV-2 DNA Vaccine INO-4800 Induces Durable Immune Responses Capable of Being Boosted in a Phase 1 Open-Label Trial** Kimberly A Kraynyak, Elliott Blackwood, Joseph Agnes, Pablo Tebas, Mary Giffear, Dinah Amante, Emma L Reuschel, Mansi Purwar, Aaron Christensen-Quick, Neiman Liu, … Mammen P Mammen Jr *The Journal of Infectious Diseases* (2022-01-25) <https://doi.org/gpdwm6> DOI: [10.1093/infdis/jiac016](https://doi.org/10.1093/infdis/jiac016) · PMID: [35079784](https://www.ncbi.nlm.nih.gov/pubmed/35079784) · PMCID: [PMC8807286](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8807286)

64. **INOVIO Announces Strategy to Address Omicron (B.1.1.529) and Future SARS-CoV-2 Variants** INOVIO Pharmaceuticals Inc <https://www.prnewswire.com/news-releases/inovio-announces-strategy-to-address-omicron-b1-1-529-and-future-sars-cov-2-variants-301433776.html>

65. **Prime-boost vaccination regimens with INO-4800 and INO-4802 augment and broaden immune responses against SARS-CoV-2 in nonhuman primates** Jewell N Walters, Blake Schouest, Ami Patel, Emma L Reuschel, Katherine Schultheis, Elizabeth Parzych, Igor Maricic, Ebony N Gary, Mansi Purwar, Viviane M Andrade, … Kate E Broderick *Vaccine* (2022-05) <https://doi.org/gp432p> DOI: [10.1016/j.vaccine.2022.03.060](https://doi.org/10.1016/j.vaccine.2022.03.060) · PMID: [35428500](https://www.ncbi.nlm.nih.gov/pubmed/35428500) · PMCID: [PMC8977452](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8977452)

66. **Design, immunogenicity and efficacy of a Pan-SARS-CoV-2 synthetic DNA vaccine** Charles C Reed, Katherine Schultheis, Viviane M Andrade, Richa Kalia, Jared Tur, Blake Schouest, Dustin Elwood, Jewell N Walters, Igor Maricic, Arthur Doan, … Kate E Broderick *Cold Spring Harbor Laboratory* (2021-05-11) <https://doi.org/gp432v> DOI: [10.1101/2021.05.11.443592](https://doi.org/10.1101/2021.05.11.443592)

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

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

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

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

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

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

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

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

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

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

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

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

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

80. **A Vaccine against Ebola Virus** Erica Ollmann Saphire *Cell* (2020-04) <https://doi.org/gprj4w> DOI: [10.1016/j.cell.2020.03.011](https://doi.org/10.1016/j.cell.2020.03.011) · PMID: [32243796](https://www.ncbi.nlm.nih.gov/pubmed/32243796)

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

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

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

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

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

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

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

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

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

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

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

92. **A single dose of ChAdOx1 MERS provides protective immunity in rhesus macaques** Neeltje van Doremalen, Elaine Haddock, Friederike Feldmann, Kimberly Meade-White, Trenton Bushmaker, Robert J Fischer, Atsushi Okumura, Patrick W Hanley, Greg Saturday, Nick J Edwards, … Vincent J Munster *Science Advances* (2020-06-12) <https://doi.org/gjkthv> DOI: [10.1126/sciadv.aba8399](https://doi.org/10.1126/sciadv.aba8399) · PMID: [32577525](https://www.ncbi.nlm.nih.gov/pubmed/32577525) · PMCID: [PMC7286676](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7286676)

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

94. **ChAdOx1 nCoV-19 vaccine prevents SARS-CoV-2 pneumonia in rhesus macaques** Neeltje van Doremalen, Teresa Lambe, Alexandra Spencer, Sandra Belij-Rammerstorfer, Jyothi N Purushotham, Julia R Port, Victoria A Avanzato, Trenton Bushmaker, Amy Flaxman, Marta Ulaszewska, … Vincent J Munster *Nature* (2020-07-30) <https://doi.org/gg67jr> DOI: [10.1038/s41586-020-2608-y](https://doi.org/10.1038/s41586-020-2608-y) · PMID: [32731258](https://www.ncbi.nlm.nih.gov/pubmed/32731258) · PMCID: [PMC8436420](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8436420)

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

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

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

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

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

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

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

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

103. **Immunogenicity and protective efficacy of one- and two-dose regimens of the Ad26.COV2.S COVID-19 vaccine candidate in adult and aged rhesus macaques** Laura Solforosi, Harmjan Kuipers, Sietske KRosendahl Huber, Joan EM van der Lubbe, Liesbeth Dekking, Dominika N Czapska-Casey, Ana Izquierdo Gil, Miranda RM Baert, Joke Drijver, Joost Vaneman, … Roland C Zahn *Cold Spring Harbor Laboratory* (2020-11-17) <https://doi.org/ghwzk9> DOI: [10.1101/2020.11.17.368258](https://doi.org/10.1101/2020.11.17.368258)

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

105. **Final Analysis of Efficacy and Safety of Single-Dose Ad26.COV2.S** Jerald Sadoff, Glenda Gray, An Vandebosch, Vicky Cárdenas, Georgi Shukarev, Beatriz Grinsztejn, Paul A Goepfert, Carla Truyers, Ilse Van Dromme, Bart Spiessens, … Macaya Douoguih *New England Journal of Medicine* (2022-03-03) <https://doi.org/gpd94g> DOI: [10.1056/nejmoa2117608](https://doi.org/10.1056/nejmoa2117608) · PMID: [35139271](https://www.ncbi.nlm.nih.gov/pubmed/35139271) · PMCID: [PMC8849184](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8849184)

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

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

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

109. **Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19** Jerald Sadoff, Glenda Gray, An Vandebosch, Vicky Cárdenas, Georgi Shukarev, Beatriz Grinsztejn, Paul A Goepfert, Carla Truyers, Hein Fennema, Bart Spiessens, … Macaya Douoguih *New England Journal of Medicine* (2021-06-10) <https://doi.org/gjsdb6> DOI: [10.1056/nejmoa2101544](https://doi.org/10.1056/nejmoa2101544) · PMID: [33882225](https://www.ncbi.nlm.nih.gov/pubmed/33882225) · PMCID: [PMC8220996](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8220996)

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

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

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

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

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

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

116. **A leading coronavirus vaccine trial is on hold: scientists react** Nicky Phillips, David Cyranoski, Smriti Mallapaty *Nature* (2020-09-09) <https://doi.org/gqbkdc> DOI: [10.1038/d41586-020-02594-w](https://doi.org/10.1038/d41586-020-02594-w) · PMID: [32908295](https://www.ncbi.nlm.nih.gov/pubmed/32908295)

117. **Scientists relieved as coronavirus vaccine trial restarts — but question lack of transparency** David Cyranoski, Smriti Mallapaty *Nature* (2020-09-14) <https://doi.org/gjf9kc> DOI: [10.1038/d41586-020-02633-6](https://doi.org/10.1038/d41586-020-02633-6) · PMID: [32929259](https://www.ncbi.nlm.nih.gov/pubmed/32929259)

118. **Blunders Eroded U.S. Confidence in Early Vaccine Front-Runner** Rebecca Robbins, Sharon LaFraniere, Noah Weiland, David D Kirkpatrick, Benjamin Mueller *The New York Times* (2020-12-08) <https://www.nytimes.com/2020/12/08/business/covid-vaccine-oxford-astrazeneca.html>

119. **Oxford/AstraZeneca Covid vaccine 'dose error' explained** BBC News (2020-11-27) <https://www.bbc.com/news/health-55086927>

120. **Fractionating a COVID-19 Ad5-vectored vaccine improves virus-specific immunity** Sarah Sanchez, Nicole Palacio, Tanushree Dangi, Thomas Ciucci, Pablo Penaloza-MacMaster *Science Immunology* (2021-12-24) <https://doi.org/gn2wwc> DOI: [10.1126/sciimmunol.abi8635](https://doi.org/10.1126/sciimmunol.abi8635) · PMID: [34648369](https://www.ncbi.nlm.nih.gov/pubmed/34648369) · PMCID: [PMC9278052](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9278052)

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

122. **The Brussels Times** <https://www.brusselstimes.com/news-contents/world/149039/1-5-million-people-have-received-sputnik-v-vaccine-russia-says-russian-direct-investment-fund-mikhail-murashko>

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

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

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

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

127. **A global database of COVID-19 vaccinations** Edouard Mathieu, Hannah Ritchie, Esteban Ortiz-Ospina, Max Roser, Joe Hasell, Cameron Appel, Charlie Giattino, Lucas Rodés-Guirao *Nature Human Behaviour* (2021-05-10) <https://doi.org/gjxxq3> DOI: [10.1038/s41562-021-01122-8](https://doi.org/10.1038/s41562-021-01122-8) · PMID: [33972767](https://www.ncbi.nlm.nih.gov/pubmed/33972767)

128. **Thrombocytopenia and Intracranial Venous Sinus Thrombosis after “COVID-19 Vaccine AstraZeneca” Exposure** Marc E Wolf, Beate Luz, Ludwig Niehaus, Pervinder Bhogal, Hansjörg Bäzner, Hans Henkes *Journal of Clinical Medicine* (2021-04-09) <https://doi.org/gmt7hb> DOI: [10.3390/jcm10081599](https://doi.org/10.3390/jcm10081599) · PMID: [33918932](https://www.ncbi.nlm.nih.gov/pubmed/33918932) · PMCID: [PMC8069989](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8069989)

129. **Covid-19: European countries suspend use of Oxford-AstraZeneca vaccine after reports of blood clots** Jacqui Wise *BMJ* (2021-03-11) <https://doi.org/gqbkdq> DOI: [10.1136/bmj.n699](https://doi.org/10.1136/bmj.n699) · PMID: [33707182](https://www.ncbi.nlm.nih.gov/pubmed/33707182)

130. **Covid-19: AstraZeneca vaccine is not linked to increased risk of blood clots, finds European Medicine Agency** Elisabeth Mahase *BMJ* (2021-03-19) <https://doi.org/gqbkdr> DOI: [10.1136/bmj.n774](https://doi.org/10.1136/bmj.n774) · PMID: [33741638](https://www.ncbi.nlm.nih.gov/pubmed/33741638)

131. **Covid-19: US suspends Johnson and Johnson vaccine rollout over blood clots** Elisabeth Mahase *BMJ* (2021-04-13) <https://doi.org/gqbkds> DOI: [10.1136/bmj.n970](https://doi.org/10.1136/bmj.n970) · PMID: [33849896](https://www.ncbi.nlm.nih.gov/pubmed/33849896)

132. **Covid-19: US authorises Johnson and Johnson vaccine again, ending pause in rollout** Janice Hopkins Tanne *BMJ* (2021-04-26) <https://doi.org/gqbkdp> DOI: [10.1136/bmj.n1079](https://doi.org/10.1136/bmj.n1079) · PMID: [33903130](https://www.ncbi.nlm.nih.gov/pubmed/33903130)

133. **Covid-19: Unusual blood clots are “very rare side effect” of Janssen vaccine, says EMA** Elisabeth Mahase *BMJ* (2021-04-21) <https://doi.org/gqbkdn> DOI: [10.1136/bmj.n1046](https://doi.org/10.1136/bmj.n1046) · PMID: [33883164](https://www.ncbi.nlm.nih.gov/pubmed/33883164)

134. **Use of the Janssen (Johnson &amp; Johnson) COVID-19 Vaccine: Updated Interim Recommendations from the Advisory Committee on Immunization Practices — United States, December 2021** Sara E Oliver, Megan Wallace, Isaac See, Sarah Mbaeyi, Monica Godfrey, Stephen C Hadler, Tara C Jatlaoui, Evelyn Twentyman, Michelle M Hughes, Agam K Rao, … Matthew F Daley *MMWR. Morbidity and Mortality Weekly Report* (2022-01-21) <https://doi.org/gn7jws> DOI: [10.15585/mmwr.mm7103a4](https://doi.org/10.15585/mmwr.mm7103a4) · PMID: [35051137](https://www.ncbi.nlm.nih.gov/pubmed/35051137) · PMCID: [PMC8774160](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8774160)

135. **Safety Monitoring of the Janssen (Johnson &amp; Johnson) COVID-19 Vaccine — United States, March–April 2021** David K Shay, Julianne Gee, John R Su, Tanya R Myers, Paige Marquez, Ruiling Liu, Bicheng Zhang, Charles Licata, Thomas A Clark, Tom T Shimabukuro *MMWR. Morbidity and Mortality Weekly Report* (2021-04-07) <https://doi.org/gm2nkf> DOI: [10.15585/mmwr.mm7018e2](https://doi.org/10.15585/mmwr.mm7018e2) · PMID: [33956784](https://www.ncbi.nlm.nih.gov/pubmed/33956784)

136. **Use of COVID-19 Vaccines After Reports of Adverse Events Among Adult Recipients of Janssen (Johnson &amp; Johnson) and mRNA COVID-19 Vaccines (Pfizer-BioNTech and Moderna): Update from the Advisory Committee on Immunization Practices — United States, July 2021** Hannah G Rosenblum, Stephen C Hadler, Danielle Moulia, Tom T Shimabukuro, John R Su, Naomi K Tepper, Kevin C Ess, Emily Jane Woo, Adamma Mba-Jonas, Meghna Alimchandani, … Sara E Oliver *MMWR. Morbidity and Mortality Weekly Report* (2021-08-13) <https://doi.org/gm2nsz> DOI: [10.15585/mmwr.mm7032e4](https://doi.org/10.15585/mmwr.mm7032e4) · PMID: [34383735](https://www.ncbi.nlm.nih.gov/pubmed/34383735) · PMCID: [PMC8360272](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8360272)

137. **Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population based cohort study** Anton Pottegård, Lars Christian Lund, Øystein Karlstad, Jesper Dahl, Morten Andersen, Jesper Hallas, Øjvind Lidegaard, German Tapia, Hanne Løvdal Gulseth, Paz Lopez-Doriga Ruiz, … Anders Hviid *BMJ* (2021-05-05) <https://doi.org/gk5nh5> DOI: [10.1136/bmj.n1114](https://doi.org/10.1136/bmj.n1114) · PMID: [33952445](https://www.ncbi.nlm.nih.gov/pubmed/33952445) · PMCID: [PMC8097496](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8097496)

138. **Risk of Vaccine-Induced Thrombotic Thrombocytopenia (VITT) following the AstraZeneca/COVISHIELD Adenovirus Vector COVID-19 Vaccines** Benjamin Chan, Ayodele Odutayo, Peter Juni, Nathan M Stall, Pavlos Bobos, Adalsteinn D Brown, Allan Grill, Noah Ivers, Antonina Maltsev, Allison McGeer, … Menaka Pai *Ontario COVID-19 Science Advisory Table* (2021-05-11) <https://doi.org/gqbkdt> DOI: [10.47326/ocsat.2021.02.28.1.0](https://doi.org/10.47326/ocsat.2021.02.28.1.0)

139. **ChAdOx1 interacts with CAR and PF4 with implications for thrombosis with thrombocytopenia syndrome** Alexander T Baker, Ryan J Boyd, Daipayan Sarkar, Alicia Teijeira-Crespo, Chun Kit Chan, Emily Bates, Kasim Waraich, John Vant, Eric Wilson, Chloe D Truong, … Mitesh J Borad *Science Advances* (2021-12-03) <https://doi.org/gpvw22> DOI: [10.1126/sciadv.abl8213](https://doi.org/10.1126/sciadv.abl8213) · PMID: [34851659](https://www.ncbi.nlm.nih.gov/pubmed/34851659) · PMCID: [PMC8635433](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8635433)

140. **Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination** Nina H Schultz, Ingvild H Sørvoll, Annika E Michelsen, Ludvig A Munthe, Fridtjof Lund-Johansen, Maria T Ahlen, Markus Wiedmann, Anne-Hege Aamodt, Thor H Skattør, Geir E Tjønnfjord, Pål A Holme *New England Journal of Medicine* (2021-06-03) <https://doi.org/gjpssx> DOI: [10.1056/nejmoa2104882](https://doi.org/10.1056/nejmoa2104882) · PMID: [33835768](https://www.ncbi.nlm.nih.gov/pubmed/33835768) · PMCID: [PMC8112568](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8112568)

141. **COVID-19 Vaccine AstraZeneca: benefits still outweigh the risks despite possible link to rare blood clots with low platelets** EMA *European Medicines Agency* (2021-03-18) <https://www.ema.europa.eu/en/news/covid-19-vaccine-astrazeneca-benefits-still-outweigh-risks-despite-possible-link-rare-blood-clots>

142. **COVID-19: Coagulopathy, Risk of Thrombosis, and the Rationale for Anticoagulation** Wolfgang Miesbach, Michael Makris *Clinical and Applied Thrombosis/Hemostasis* (2020-01-01) <https://doi.org/gjvk4t> DOI: [10.1177/1076029620938149](https://doi.org/10.1177/1076029620938149) · PMID: [32677459](https://www.ncbi.nlm.nih.gov/pubmed/32677459) · PMCID: [PMC7370334](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7370334)

143. **Three decades of messenger RNA vaccine development** Rein Verbeke, Ine Lentacker, Stefaan C De Smedt, Heleen Dewitte *Nano Today* (2019-10) <https://doi.org/ghm43s> DOI: [10.1016/j.nantod.2019.100766](https://doi.org/10.1016/j.nantod.2019.100766)

144. **Developing mRNA-vaccine technologies** Thomas Schlake, Andreas Thess, Mariola Fotin-Mleczek, Karl-Josef Kallen *RNA Biology* (2012-11) <https://doi.org/f4qzdb> DOI: [10.4161/rna.22269](https://doi.org/10.4161/rna.22269) · PMID: [23064118](https://www.ncbi.nlm.nih.gov/pubmed/23064118) · PMCID: [PMC3597572](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3597572)

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

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

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

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

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

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

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

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

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

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

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

156. **Managing intellectual property to develop medicines for the world's poorest** Sylvie Fonteilles-Drabek, David Reddy, Timothy NC Wells *Nature Reviews Drug Discovery* (2017-02-24) <https://doi.org/gmqmgv> DOI: [10.1038/nrd.2017.24](https://doi.org/10.1038/nrd.2017.24) · PMID: [28232725](https://www.ncbi.nlm.nih.gov/pubmed/28232725)

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

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

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

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

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

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

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

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

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

166. **Prevention and Attenuation of Covid-19 with the BNT162b2 and mRNA-1273 Vaccines** Mark G Thompson, Jefferey L Burgess, Allison L Naleway, Harmony Tyner, Sarang K Yoon, Jennifer Meece, Lauren EW Olsho, Alberto J Caban-Martinez, Ashley L Fowlkes, Karen Lutrick, … Manjusha Gaglani *New England Journal of Medicine* (2021-07-22) <https://doi.org/gk3bzr> DOI: [10.1056/nejmoa2107058](https://doi.org/10.1056/nejmoa2107058) · PMID: [34192428](https://www.ncbi.nlm.nih.gov/pubmed/34192428) · PMCID: [PMC8262622](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8262622)

167. **Increased risk of SARS-CoV-2 reinfection associated with emergence of Omicron in South Africa** Juliet RC Pulliam, Cari van Schalkwyk, Nevashan Govender, Anne von Gottberg, Cheryl Cohen, Michelle J Groome, Jonathan Dushoff, Koleka Mlisana, Harry Moultrie *Cold Spring Harbor Laboratory* (2021-11-11) <https://doi.org/g8gj> DOI: [10.1101/2021.11.11.21266068](https://doi.org/10.1101/2021.11.11.21266068)

168. **2022-07-15 12:20 | Archive of CDC Covid Pages** <https://public4.pagefreezer.com/browse/CDC%20Covid%20Pages/15-07-2022T12:20/https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/scientific-brief-omicron-variant.html>

169. **Sensitivity of infectious SARS-CoV-2 B.1.1.7 and B.1.351 variants to neutralizing antibodies** Delphine Planas, Timothée Bruel, Ludivine Grzelak, Florence Guivel-Benhassine, Isabelle Staropoli, Françoise Porrot, Cyril Planchais, Julian Buchrieser, Maaran Michael Rajah, Elodie Bishop, … Olivier Schwartz *Nature Medicine* (2021-03-26) <https://doi.org/gjmwwr> DOI: [10.1038/s41591-021-01318-5](https://doi.org/10.1038/s41591-021-01318-5) · PMID: [33772244](https://www.ncbi.nlm.nih.gov/pubmed/33772244)

170. **Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7** Pengfei Wang, Manoj S Nair, Lihong Liu, Sho Iketani, Yang Luo, Yicheng Guo, Maple Wang, Jian Yu, Baoshan Zhang, Peter D Kwong, … David D Ho *Nature* (2021-03-08) <https://doi.org/gjhdxm> DOI: [10.1038/s41586-021-03398-2](https://doi.org/10.1038/s41586-021-03398-2) · PMID: [33684923](https://www.ncbi.nlm.nih.gov/pubmed/33684923)

171. **Neutralizing Antibodies Against SARS-CoV-2 Variants After Infection and Vaccination** Venkata Viswanadh Edara, William H Hudson, Xuping Xie, Rafi Ahmed, Mehul S Suthar *JAMA* (2021-05-11) <https://doi.org/gj29vq> DOI: [10.1001/jama.2021.4388](https://doi.org/10.1001/jama.2021.4388) · PMID: [33739374](https://www.ncbi.nlm.nih.gov/pubmed/33739374) · PMCID: [PMC7980146](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7980146)

172. **Classification of Omicron (B.1.1.529): SARS-CoV-2 Variant of Concern** <https://www.who.int/news/item/26-11-2021-classification-of-omicron-(b.1.1.529)-sars-cov-2-variant-of-concern>

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

174. **Breakthrough Infections with SARS-CoV-2 Omicron Variant Despite Booster Dose of mRNA Vaccine** Constanze Kuhlmann, Carla Konstanze Mayer, Mathilda Claassen, Tongai G Maponga, Andrew D Sutherland, Tasnim Suliman, Megan Shaw, Wolfgang Preiser *SSRN Electronic Journal* (2021) <https://doi.org/gpnbfz> DOI: [10.2139/ssrn.3981711](https://doi.org/10.2139/ssrn.3981711)

175. **Coronavirus in the U.S.: Latest Map and Case Count** The New York Times <https://www.nytimes.com/interactive/2021/us/covid-cases.html>

176. **Analysis | Four charts that analyze how omicron’s wave compares to previous coronavirus peaks** Shelly Tan *Washington Post* <https://www.washingtonpost.com/health/interactive/2022/omicron-comparison-cases-deaths-hospitalizations/>

177. **SARS-CoV-2 Omicron: evasion of potent humoral responses and resistance to clinical immunotherapeutics relative to viral variants of concern** Anupriya Aggarwal, Alberto Ospina Stella, Gregory Walker, Anouschka Akerman, Vanessa Milogiannakis, Fabienne Brilot, Supavadee Amatayakul-Chantler, Nathan Roth, Germano Coppola, Peter Schofield, … Stuart Turville *Cold Spring Harbor Laboratory* (2021-12-15) <https://doi.org/hb73> DOI: [10.1101/2021.12.14.21267772](https://doi.org/10.1101/2021.12.14.21267772)

178. **Effectiveness of BNT162b2 Vaccine against Omicron Variant in South Africa** Shirley Collie, Jared Champion, Harry Moultrie, Linda-Gail Bekker, Glenda Gray *New England Journal of Medicine* (2022-02-03) <https://doi.org/gnxj2w> DOI: [10.1056/nejmc2119270](https://doi.org/10.1056/nejmc2119270) · PMID: [34965358](https://www.ncbi.nlm.nih.gov/pubmed/34965358) · PMCID: [PMC8757569](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8757569)

179. **A meta-analysis of Early Results to predict Vaccine efficacy against Omicron** David S Khoury, Megan Steain, James A Triccas, Alex Sigal, Miles P Davenport, Deborah Cromer *Cold Spring Harbor Laboratory* (2021-12-14) <https://doi.org/gpnbd5> DOI: [10.1101/2021.12.13.21267748](https://doi.org/10.1101/2021.12.13.21267748)

180. **Waning 2-Dose and 3-Dose Effectiveness of mRNA Vaccines Against COVID-19–Associated Emergency Department and Urgent Care Encounters and Hospitalizations Among Adults During Periods of Delta and Omicron Variant Predominance — VISION Network, 10 States, August 2021–January 2022** Jill M Ferdinands, Suchitra Rao, Brian E Dixon, Patrick K Mitchell, Malini B DeSilva, Stephanie A Irving, Ned Lewis, Karthik Natarajan, Edward Stenehjem, Shaun J Grannis, … Bruce Fireman *MMWR. Morbidity and Mortality Weekly Report* (2022-02-18) <https://doi.org/gpfrkh> DOI: [10.15585/mmwr.mm7107e2](https://doi.org/10.15585/mmwr.mm7107e2) · PMID: [35176007](https://www.ncbi.nlm.nih.gov/pubmed/35176007) · PMCID: [PMC8853475](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8853475)

181. **COVID-19 mRNA booster vaccines elicit strong protection against SARS-CoV-2 Omicron variant in patients with cancer** Cong Zeng, John P Evans, Karthik Chakravarthy, Panke Qu, Sarah Reisinger, No-Joon Song, Mark P Rubinstein, Peter G Shields, Zihai Li, Shan-Lu Liu *Cancer Cell* (2022-02) <https://doi.org/gn2gcf> DOI: [10.1016/j.ccell.2021.12.014](https://doi.org/10.1016/j.ccell.2021.12.014) · PMID: [34986328](https://www.ncbi.nlm.nih.gov/pubmed/34986328) · PMCID: [PMC8716174](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8716174)

182. **Immune correlates analysis of the mRNA-1273 COVID-19 vaccine efficacy clinical trial** Peter B Gilbert, David C Montefiori, Adrian B McDermott, Youyi Fong, David Benkeser, Weiping Deng, Honghong Zhou, Christopher R Houchens, Karen Martins, Lakshmi Jayashankar, … *Science* (2022-01-07) <https://doi.org/gpnbff> DOI: [10.1126/science.abm3425](https://doi.org/10.1126/science.abm3425) · PMID: [34812653](https://www.ncbi.nlm.nih.gov/pubmed/34812653) · PMCID: [PMC9017870](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9017870)

183. **Towards a population-based threshold of protection for COVID-19 vaccines** David Goldblatt, Andrew Fiore-Gartland, Marina Johnson, Adam Hunt, Christopher Bengt, Dace Zavadska, Hilda Darta Snipe, Jeremy S Brown, Lesley Workman, Heather J Zar, … Donna Ambrosino *Vaccine* (2022-01) <https://doi.org/gpnbdz> DOI: [10.1016/j.vaccine.2021.12.006](https://doi.org/10.1016/j.vaccine.2021.12.006) · PMID: [34933765](https://www.ncbi.nlm.nih.gov/pubmed/34933765) · PMCID: [PMC8673730](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8673730)

184. **Evidence for antibody as a protective correlate for COVID-19 vaccines** Kristen A Earle, Donna M Ambrosino, Andrew Fiore-Gartland, David Goldblatt, Peter B Gilbert, George R Siber, Peter Dull, Stanley A Plotkin *Vaccine* (2021-07) <https://doi.org/gnr5w7> DOI: [10.1016/j.vaccine.2021.05.063](https://doi.org/10.1016/j.vaccine.2021.05.063) · PMID: [34210573](https://www.ncbi.nlm.nih.gov/pubmed/34210573) · PMCID: [PMC8142841](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8142841)

185. **Towards Internationally standardised humoral Immune Correlates of Protection from SARS-CoV-2 infection and COVID-19 disease** Javier Castillo-Olivares, David A Wells, Matteo Ferrari, Andrew Chan, Peter Smith, Angalee Nadesalingam, Minna Paloniemi, George Carnell, Luis Ohlendorf, Diego Cantoni, … Jonathan Heeney *Cold Spring Harbor Laboratory* (2021-05-23) <https://doi.org/gk7czq> DOI: [10.1101/2021.05.21.21257572](https://doi.org/10.1101/2021.05.21.21257572)

186. **A longitudinal study of SARS-CoV-2-infected patients reveals a high correlation between neutralizing antibodies and COVID-19 severity** Vincent Legros, Solène Denolly, Manon Vogrig, Bertrand Boson, Eglantine Siret, Josselin Rigaill, Sylvie Pillet, Florence Grattard, Sylvie Gonzalo, Paul Verhoeven, … Bruno Pozzetto *Cellular &amp; Molecular Immunology* (2021-01-06) <https://doi.org/gh5qjr> DOI: [10.1038/s41423-020-00588-2](https://doi.org/10.1038/s41423-020-00588-2) · PMID: [33408342](https://www.ncbi.nlm.nih.gov/pubmed/33408342) · PMCID: [PMC7786875](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7786875)

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

188. **Predicting Influenza H3N2 Vaccine Efficacy From Evolution of the Dominant Epitope** Melia E Bonomo, Michael W Deem *Clinical Infectious Diseases* (2018-04-17) <https://doi.org/gf33js> DOI: [10.1093/cid/ciy323](https://doi.org/10.1093/cid/ciy323) · PMID: [29672670](https://www.ncbi.nlm.nih.gov/pubmed/29672670)

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

190. **Efficacy and Safety of a Booster Regimen of Ad26.COV2.S Vaccine against Covid-19** Karin Hardt, An Vandebosch, Jerry Sadoff, Mathieu Le Gars, Carla Truyers, David Lowson, Ilse Van Dromme, Johan Vingerhoets, Tobias Kamphuis, Gert Scheper, … *Cold Spring Harbor Laboratory* (2022-01-31) <https://doi.org/gqbkdm> DOI: [10.1101/2022.01.28.22270043](https://doi.org/10.1101/2022.01.28.22270043)

191. **Sputnik Light booster after Sputnik V vaccination induces robust neutralizing antibody response to B.1.1.529 (Omicron) SARS-CoV-2 variant** IV Dolzhikova, AA Iliukhina, AV Kovyrshina, AV Kuzina, VA Gushchin, AE Siniavin, AA Pochtovyi, EV Shidlovskaya, NA Kuznetsova, MM Megeryan, … AL Gintsburg *Cold Spring Harbor Laboratory* (2021-12-21) <https://doi.org/gqbkdk> DOI: [10.1101/2021.12.17.21267976](https://doi.org/10.1101/2021.12.17.21267976)

192. **Reactogenicity and immunogenicity after a late second dose or a third dose of ChAdOx1 nCoV-19 in the UK: a substudy of two randomised controlled trials (COV001 and COV002)** Amy Flaxman, Natalie G Marchevsky, Daniel Jenkin, Jeremy Aboagye, Parvinder K Aley, Brian Angus, Sandra Belij-Rammerstorfer, Sagida Bibi, Mustapha Bittaye, Federica Cappuccini, … Andy Yao *The Lancet* (2021-09) <https://doi.org/hx9c> DOI: [10.1016/s0140-6736(21)01699-8](https://doi.org/10.1016/s0140-6736(21)01699-8) · PMID: [34480858](https://www.ncbi.nlm.nih.gov/pubmed/34480858) · PMCID: [PMC8409975](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8409975)

193. **4th Dose COVID mRNA Vaccines’ Immunogenicity &amp; Efficacy Against Omicron VOC** Gili Regev-Yochay, Tal Gonen, Mayan Gilboa, Michal Mandelboim, Victoria Indenbaum, Sharon Amit, Lilac Meltzer, Keren Asraf, Carmit Cohen, Ronen Fluss, … Yaniv Lustig *Cold Spring Harbor Laboratory* (2022-02-15) <https://doi.org/gpnbfd> DOI: [10.1101/2022.02.15.22270948](https://doi.org/10.1101/2022.02.15.22270948)

194. **To mix or not to mix? A rapid systematic review of heterologous prime–boost covid-19 vaccination** Nan-Chang Chiu, Hsin Chi, Yu-Kang Tu, Ya-Ning Huang, Yu-Lin Tai, Shun-Long Weng, Lung Chang, Daniel Tsung-Ning Huang, Fu-Yuan Huang, Chien-Yu Lin *Expert Review of Vaccines* (2021-09-01) <https://doi.org/gqbkdd> DOI: [10.1080/14760584.2021.1971522](https://doi.org/10.1080/14760584.2021.1971522) · PMID: [34415818](https://www.ncbi.nlm.nih.gov/pubmed/34415818) · PMCID: [PMC8425437](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8425437)

195. **Homologous and Heterologous Covid-19 Booster Vaccinations** Robert L Atmar, Kirsten E Lyke, Meagan E Deming, Lisa A Jackson, Angela R Branche, Hana M El Sahly, Christina A Rostad, Judith M Martin, Christine Johnston, Richard E Rupp, … John H Beigel *New England Journal of Medicine* (2022-03-17) <https://doi.org/gn9v3v> DOI: [10.1056/nejmoa2116414](https://doi.org/10.1056/nejmoa2116414) · PMID: [35081293](https://www.ncbi.nlm.nih.gov/pubmed/35081293) · PMCID: [PMC8820244](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8820244)

196. **Effectiveness of homologous and heterologous booster doses for an inactivated SARS-CoV-2 vaccine: a large-scale prospective cohort study** Alejandro Jara, Eduardo A Undurraga, José R Zubizarreta, Cecilia González, Alejandra Pizarro, Johanna Acevedo, Katherinne Leo, Fabio Paredes, Tomás Bralic, Verónica Vergara, … Rafael Araos *The Lancet Global Health* (2022-06) <https://doi.org/hzck> DOI: [10.1016/s2214-109x(22)00112-7](https://doi.org/10.1016/s2214-109x(22)00112-7) · PMID: [35472300](https://www.ncbi.nlm.nih.gov/pubmed/35472300) · PMCID: [PMC9034854](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9034854)

197. **Heterologous prime–boost strategies for COVID-19 vaccines** Binaya Sapkota, Bhuvan Saud, Ranish Shrestha, Dhurgham Al-Fahad, Ranjit Sah, Sunil Shrestha, Alfonso J Rodriguez-Morales *Journal of Travel Medicine* (2021-12-16) <https://doi.org/gqbkdg> DOI: [10.1093/jtm/taab191](https://doi.org/10.1093/jtm/taab191) · PMID: [34918097](https://www.ncbi.nlm.nih.gov/pubmed/34918097) · PMCID: [PMC8754745](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8754745)

198. **Neutralizing Activities Against the Omicron Variant After a Heterologous Booster in Healthy Adults Receiving Two Doses of CoronaVac Vaccination** Suvichada Assawakosri, Sitthichai Kanokudom, Nungruthai Suntronwong, Chompoonut Auphimai, Pornjarim Nilyanimit, Preeyaporn Vichaiwattana, Thanunrat Thongmee, Thaneeya Duangchinda, Warangkana Chantima, Pattarakul Pakchotanon, … Yong Poovorawan *The Journal of Infectious Diseases* (2022-03-10) <https://doi.org/gqbkdf> DOI: [10.1093/infdis/jiac092](https://doi.org/10.1093/infdis/jiac092) · PMID: [35267040](https://www.ncbi.nlm.nih.gov/pubmed/35267040)

199. **Effectiveness of Homologous and Heterologous Covid-19 Boosters against Omicron** Emma K Accorsi, Amadea Britton, Nong Shang, Katherine E Fleming-Dutra, Ruth Link-Gelles, Zachary R Smith, Gordana Derado, Joseph Miller, Stephanie J Schrag, Jennifer R Verani *New England Journal of Medicine* (2022-06-23) <https://doi.org/gp8d5h> DOI: [10.1056/nejmc2203165](https://doi.org/10.1056/nejmc2203165) · PMID: [35613039](https://www.ncbi.nlm.nih.gov/pubmed/35613039) · PMCID: [PMC9165559](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9165559)

200. **Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial** Alasdair PS Munro, Leila Janani, Victoria Cornelius, Parvinder K Aley, Gavin Babbage, David Baxter, Marcin Bula, Katrina Cathie, Krishna Chatterjee, Kate Dodd, … Kim Appleby *The Lancet* (2021-12) <https://doi.org/gnpjxm> DOI: [10.1016/s0140-6736(21)02717-3](https://doi.org/10.1016/s0140-6736(21)02717-3) · PMID: [34863358](https://www.ncbi.nlm.nih.gov/pubmed/34863358) · PMCID: [PMC8639161](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8639161)

201. **Overview of EU/EEA country recommendations on COVID-19 vaccination with Vaxzevria, and a scoping review of evidence to guide decision-making** European Centre for Disease Prevention and Control (2021-05-18) <https://www.ecdc.europa.eu/en/publications-data/overview-eueea-country-recommendations-covid-19-vaccination-vaxzevria-and-scoping>

202. **Heterologous vaccine regimens against COVID-19** Talita Duarte-Salles, Daniel Prieto-Alhambra *The Lancet* (2021-07) <https://doi.org/hzcc> DOI: [10.1016/s0140-6736(21)01442-2](https://doi.org/10.1016/s0140-6736(21)01442-2) · PMID: [34181881](https://www.ncbi.nlm.nih.gov/pubmed/34181881) · PMCID: [PMC8233006](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8233006)

203. **Moderna Announces Omicron-Containing Bivalent Booster Candidate mRNA-1273.214 Demonstrates Superior Antibody Response Against Omicron** <https://investors.modernatx.com/news/news-details/2022/Moderna-Announces-Omicron-Containing-Bivalent-Booster-Candidate-mRNA-1273.214-Demonstrates-Superior-Antibody-Response-Against-Omicron/default.aspx>

204. **Viral dynamics in asymptomatic patients with COVID-19** Rui Zhou, Furong Li, Fengjuan Chen, Huamin Liu, Jiazhen Zheng, Chunliang Lei, Xianbo Wu *International Journal of Infectious Diseases* (2020-07) <https://doi.org/ggxs96> DOI: [10.1016/j.ijid.2020.05.030](https://doi.org/10.1016/j.ijid.2020.05.030) · PMID: [32437933](https://www.ncbi.nlm.nih.gov/pubmed/32437933) · PMCID: [PMC7211726](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7211726)

205. **Higher viral loads in asymptomatic COVID-19 patients might be the invisible part of the iceberg** Imran Hasanoglu, Gulay Korukluoglu, Dilek Asilturk, Yasemin Cosgun, Ayse Kaya Kalem, Ayşe Basak Altas, Bircan Kayaaslan, Fatma Eser, Esra Akkan Kuzucu, Rahmet Guner *Infection* (2020-11-24) <https://doi.org/ghxsp4> DOI: [10.1007/s15010-020-01548-8](https://doi.org/10.1007/s15010-020-01548-8) · PMID: [33231841](https://www.ncbi.nlm.nih.gov/pubmed/33231841) · PMCID: [PMC7685188](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7685188)

206. **Relationships between Viral Load and the Clinical Course of COVID-19** Hiroyuki Tsukagoshi, Daisuke Shinoda, Mariko Saito, Kaori Okayama, Mitsuru Sada, Hirokazu Kimura, Nobuhiro Saruki *Viruses* (2021-02-15) <https://doi.org/gndc5c> DOI: [10.3390/v13020304](https://doi.org/10.3390/v13020304) · PMID: [33672005](https://www.ncbi.nlm.nih.gov/pubmed/33672005) · PMCID: [PMC7919281](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7919281)

207. **Estimating the extent of asymptomatic COVID-19 and its potential for community transmission: Systematic review and meta-analysis** Oyungerel Byambasuren, Magnolia Cardona, Katy Bell, Justin Clark, Mary-Louise McLaws, Paul Glasziou *Official Journal of the Association of Medical Microbiology and Infectious Disease Canada* (2020-12-31) <https://doi.org/gh7qmm> DOI: [10.3138/jammi-2020-0030](https://doi.org/10.3138/jammi-2020-0030)

208. **SARS-CoV-2 Infection after Vaccination in Health Care Workers in California** Jocelyn Keehner, Lucy E Horton, Michael A Pfeffer, Christopher A Longhurst, Robert T Schooley, Judith S Currier, Shira R Abeles, Francesca J Torriani *New England Journal of Medicine* (2021-05-06) <https://doi.org/gjjr6h> DOI: [10.1056/nejmc2101927](https://doi.org/10.1056/nejmc2101927) · PMID: [33755376](https://www.ncbi.nlm.nih.gov/pubmed/33755376) · PMCID: [PMC8008750](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8008750)

209. **Impact of the Coronavirus Disease 2019 (COVID-19) Vaccine on Asymptomatic Infection Among Patients Undergoing Preprocedural COVID-19 Molecular Screening** Aaron J Tande, Benjamin D Pollock, Nilay D Shah, Gianrico Farrugia, Abinash Virk, Melanie Swift, Laura Breeher, Matthew Binnicker, Elie F Berbari *Clinical Infectious Diseases* (2021-03-10) <https://doi.org/gjg8qf> DOI: [10.1093/cid/ciab229](https://doi.org/10.1093/cid/ciab229) · PMID: [33704435](https://www.ncbi.nlm.nih.gov/pubmed/33704435) · PMCID: [PMC7989519](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7989519)

210. **Association Between Vaccination With BNT162b2 and Incidence of Symptomatic and Asymptomatic SARS-CoV-2 Infections Among Health Care Workers** Yoel Angel, Avishay Spitzer, Oryan Henig, Esther Saiag, Eli Sprecher, Hagit Padova, Ronen Ben-Ami *JAMA* (2021-06-22) <https://doi.org/gjwp6b> DOI: [10.1001/jama.2021.7152](https://doi.org/10.1001/jama.2021.7152) · PMID: [33956048](https://www.ncbi.nlm.nih.gov/pubmed/33956048) · PMCID: [PMC8220476](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8220476)

211. **Initial report of decreased SARS-CoV-2 viral load after inoculation with the BNT162b2 vaccine** Matan Levine-Tiefenbrun, Idan Yelin, Rachel Katz, Esma Herzel, Ziv Golan, Licita Schreiber, Tamar Wolf, Varda Nadler, Amir Ben-Tov, Jacob Kuint, … Roy Kishony *Nature Medicine* (2021-03-29) <https://doi.org/gjmx9h> DOI: [10.1038/s41591-021-01316-7](https://doi.org/10.1038/s41591-021-01316-7) · PMID: [33782619](https://www.ncbi.nlm.nih.gov/pubmed/33782619)

212. **Virological and serological kinetics of SARS-CoV-2 Delta variant vaccine-breakthrough infections: a multi-center cohort study** Po Ying Chia, Sean Wei Xiang Ong, Calvin J Chiew, Li Wei Ang, Jean-Marc Chavatte, Tze-Minn Mak, Lin Cui, Shirin Kalimuddin, Wan Ni Chia, Chee Wah Tan, … Barnaby Edward Young *Cold Spring Harbor Laboratory* (2021-07-31) <https://doi.org/gmd72x> DOI: [10.1101/2021.07.28.21261295](https://doi.org/10.1101/2021.07.28.21261295)

213. **Shedding of Infectious SARS-CoV-2 Despite Vaccination** Kasen K Riemersma, Luis A Haddock III, Nancy A Wilson, Nicholas Minor, Jens Eickhoff, Brittany E Grogan, Amanda Kita-Yarbro, Peter J Halfmann, Hannah E Segaloff, Anna Kocharian, … Katarina M Grande *Cold Spring Harbor Laboratory* (2021-07-31) <https://doi.org/gmfh6j> DOI: [10.1101/2021.07.31.21261387](https://doi.org/10.1101/2021.07.31.21261387)

214. **No Significant Difference in Viral Load Between Vaccinated and Unvaccinated, Asymptomatic and Symptomatic Groups When Infected with SARS-CoV-2 Delta Variant** Charlotte B Acharya, John Schrom, Anthea M Mitchell, David A Coil, Carina Marquez, Susana Rojas, Chung Yu Wang, Jamin Liu, Genay Pilarowski, Leslie Solis, … Diane Havlir *Cold Spring Harbor Laboratory* (2021-09-29) <https://doi.org/gndc47> DOI: [10.1101/2021.09.28.21264262](https://doi.org/10.1101/2021.09.28.21264262)

215. **Editorial: Reverse Vaccinology** Richard Moxon, Pedro A Reche, Rino Rappuoli *Frontiers in Immunology* (2019-12-03) <https://doi.org/gjjtwg> DOI: [10.3389/fimmu.2019.02776](https://doi.org/10.3389/fimmu.2019.02776) · PMID: [31849959](https://www.ncbi.nlm.nih.gov/pubmed/31849959) · PMCID: [PMC6901788](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6901788)

216. **Rapid response to an emerging infectious disease – Lessons learned from development of a synthetic DNA vaccine targeting Zika virus** Sagar B Kudchodkar, Hyeree Choi, Emma L Reuschel, Rianne Esquivel, Jackie Jin-Ah Kwon, Moonsup Jeong, Joel N Maslow, Charles C Reed, Scott White, JJoseph Kim, … Kar Muthumani *Microbes and Infection* (2018-12) <https://doi.org/gfrn5h> DOI: [10.1016/j.micinf.2018.03.001](https://doi.org/10.1016/j.micinf.2018.03.001) · PMID: [29555345](https://www.ncbi.nlm.nih.gov/pubmed/29555345) · PMCID: [PMC6593156](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6593156)

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

218. **Safety and Immunogenicity of a DNA SARS-CoV-2 vaccine (ZyCoV-D): Results of an open-label, non-randomized phase I part of phase I/II clinical study by intradermal route in healthy subjects in India** Taufik Momin, Kevinkumar Kansagra, Hardik Patel, Sunil Sharma, Bhumika Sharma, Jatin Patel, Ravindra Mittal, Jayesh Sanmukhani, Kapil Maithal, Ayan Dey, … Deven Parmar *EClinicalMedicine* (2021-08) <https://doi.org/gmx9rv> DOI: [10.1016/j.eclinm.2021.101020](https://doi.org/10.1016/j.eclinm.2021.101020) · PMID: [34308319](https://www.ncbi.nlm.nih.gov/pubmed/34308319) · PMCID: [PMC8285262](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8285262)

219. **Comparative Effectiveness of Moderna, Pfizer-BioNTech, and Janssen (Johnson &amp; Johnson) Vaccines in Preventing COVID-19 Hospitalizations Among Adults Without Immunocompromising Conditions — United States, March–August 2021** Wesley H Self, Mark W Tenforde, Jillian P Rhoads, Manjusha Gaglani, Adit A Ginde, David J Douin, Samantha M Olson, HKeipp Talbot, Jonathan D Casey, Nicholas M Mohr, … *MMWR. Morbidity and Mortality Weekly Report* (2021-09-24) <https://doi.org/gmwmt8> DOI: [10.15585/mmwr.mm7038e1](https://doi.org/10.15585/mmwr.mm7038e1) · PMID: [34555004](https://www.ncbi.nlm.nih.gov/pubmed/34555004) · PMCID: [PMC8459899](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8459899)

220. **Where a Vast Global Vaccination Program Went Wrong** Benjamin Mueller, Rebecca Robbins *The New York Times* (2021-08-02) <https://www.nytimes.com/2021/08/02/world/europe/covax-covid-vaccine-problems-africa.html>

221. **Innovators target vaccines for variants and shortages in global South** Cormac Sheridan *Nature Biotechnology* (2021-03-17) <https://doi.org/gk68d7> DOI: [10.1038/d41587-021-00001-x](https://doi.org/10.1038/d41587-021-00001-x) · PMID: [33731936](https://www.ncbi.nlm.nih.gov/pubmed/33731936)

222. **Does the World Still Need New Covid-19 Vaccines?** Hanna Nohynek, Annelies Wilder-Smith *New England Journal of Medicine* (2022-06-02) <https://doi.org/gqbkkz> DOI: [10.1056/nejme2204695](https://doi.org/10.1056/nejme2204695) · PMID: [35507476](https://www.ncbi.nlm.nih.gov/pubmed/35507476) · PMCID: [PMC9093715](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9093715)