



COVID-19 Vaccines

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Introduction

Over the last year, multiple vaccines capable of preventing symptomatic COVID-19 have been developed in record time (see table below). The achievement is a testament to the commitment of all involved including scientists, pharmaceutical companies, medical staff, community members and hundreds of thousands of volunteer participants. Efficacy has varied, but there's encouraging consistency in vaccine prevention of the most serious COVID-19 outcomes of hospitalization and death. [Emerging evidence](#) suggests vaccines may also be able to significantly reduce the incidence of asymptomatic infection with SARS-CoV-2, but additional studies addressing this issue are ongoing. Prevention of asymptomatic infection would allow vaccination to reduce SARS-CoV-2 transmission as well as symptomatic disease.

Vaccine rollout is now underway in many places, but there are clear inequities with wealthier nations corraling much of the supply and efforts to expand access in resource-limited settings only just beginning to make headway. Disparities [are also apparent within the United States](#), with vaccination of Black and Hispanic/Latinx people lagging compared to the White population.

The pipeline of experimental COVID-19 vaccines remains robust, but it's unclear to what extent additional candidates will be needed. Currently, there's greater focus on the possibility that modifications will be required for available vaccines to ensure efficacy against emerging variants of SARS-CoV-2, some of which show reduced susceptibility to antibody responses induced by first generation products. The U.S. Food and Drug Administration (FDA) has [updated their guidance for manufacturers](#), allowing for the possibility of authorizing modified vaccines based on demonstrating the induction of immune responses comparable to the parent construct.

For current information on the COVID-19 vaccine pipeline we recommend the online trackers available from the [World Health Organization](#) (WHO), the [New York Times](#) and [Regulatory Focus](#). The impressive *New York Times* resource also includes detailed

information on the locations where each vaccine has been authorized for use. AVAC's vaccine [cheat sheet](#) offers an accessible summary of the pipeline and the types of technologies being employed to create vaccines.

History

Scientists began designing vaccines and initiating clinical trials almost immediately after the COVID-19 crisis began. The effort benefited greatly from the latest microbiological tools, which allowed rapid sequencing of the SARS-CoV-2 genome. Evidence implicated the virus's spike protein as the [key target](#) for the immune system, and the gene sequence encoding the protein was quickly available to vaccine manufacturers (the SARS-CoV-2 genome sequence was [shared publicly](#) by researchers in China on January 10, 2020).

The majority of vaccines have utilized a modified "prefusion" version of the SARS-CoV-2 spike protein collaboratively developed by US-based researchers as part of [pandemic preparedness efforts](#) during the Obama administration. The design of the prefusion spike protein antigen was [made possible](#) by the efforts of researchers to develop a stable form of the HIV Envelope protein. The approach was [initially applied](#) to a spike protein from the coronavirus that caused Middle East respiratory syndrome, allowing it to be rapidly and successfully translated to SARS-CoV-2. The prefusion spike protein antigen has enhanced stability and appears to induce superior antibody responses compared to the unmodified form. The Vaccine Research Center at the National Institutes of Health, which was founded by Bill Clinton in the late 1990s to work on HIV vaccine development, played a leading role in this work.

Immunity Against SARS-CoV-2

The welcome news that multiple COVID-19 vaccine candidates have demonstrated efficacy represents direct evidence that protective immunity against SARS-CoV-2 is possible. The duration of vaccine-induced protective immunity remains an important question, which will need to be answered by [continued follow up](#) of participants in ongoing efficacy trials and assessments of the real-world impact of vaccine rollout. Analyses will also try to discern if there were specific types of vaccine-induced immune responses that correlated with protection against COVID-19 disease and/or SARS-CoV-2 infection. Identifying correlates of immunity would greatly assist efforts to develop additional vaccines.

Antibody and T-cell responses are considered the most likely contributors to protective immunity. Antibodies are Y-shaped proteins made by white blood cells called B cells in response to an infection. These molecules (including antibodies called IgG and IgA) are used to target a virus or bacterium for destruction upon reinfection, often leading to protection against that pathogen. A [comprehensive review of the literature](#) on antibody

responses to coronaviruses suggests that several measures may be possible correlates of immunity including serum (blood) IgG and IgA, mucosal IgA, and neutralizing antibody titers.

Neutralizing antibodies specifically inhibit pathogen replication and are likely to be a major focus of efforts to discern which vaccine-induced immune responses correlated with protection against COVID-19 disease and/or SARS-CoV-2 infection. Multiple studies of COVID-19 vaccine candidates in macaques have demonstrated that neutralizing antibody responses against the SARS-CoV-2 spike protein were [the key parameter](#) associated with protection against COVID-19 disease.

T cells are another type of white blood cell that play a critical role in responding to infection. Scientific literature is now accumulating demonstrating [robust induction](#) of SARS-CoV-2-specific CD4 and CD8 T cell responses in almost all infected people. T cell responses have also been detected in some [exposed but antibody seronegative](#) individuals.

Encouragingly, studies have documented the [persistence of immunological memory](#) against SARS-CoV-2 among people who recovered from the infection. The responses consisted of memory B cells and T cells which are poised to react quickly if the virus is encountered a second time. The findings offer hope that vaccines will induce similarly persistent memory responses.

Reasons for Caution

In a number of experimental settings involving other coronaviruses, a phenomenon of antibody-dependent enhancement (ADE) of disease has been described, in which vaccine-induced antibodies interact with the virus in ways that promote (rather than protect against) tissue damage. Thankfully, the results from COVID-19 vaccine efficacy trials show no evidence of ADE.

Scientists are currently monitoring whether genetic variation of SARS-CoV-2 could reduce or eliminate efficacy of currently available vaccines. The genome of SARS-CoV-2 is [relatively stable](#) compared to many other RNA viruses, but variants have emerged around the globe that show reduced susceptibility to vaccine-induced neutralizing antibody responses. Currently, the evidence suggests that vaccines create high enough antibody levels to maintain protection in most cases. However, one example has been reported of a vaccine failing to show efficacy in South Africa, where a SARS-CoV-2 variant with reduced susceptibility to common antibody responses has become preponderant (see table entry on the AstraZeneca vaccine below). The scientist and writer Eric Topol is posting a [regularly updated table](#) with information on the major SARS-CoV-2 variants on this [twitter feed](#).

Concerns have been raised about the possibility of reinfection with SARS-CoV-2. Initially, this was based on anecdotal reports but there are now [multiple cases](#) where researchers have documented compelling evidence of reinfection based on genetic sequencing of the viruses responsible for the first and second infections. The frequency of the phenomenon [appears very low](#), and any implications for vaccines are as yet unclear.

The duration of vaccine-induced protective immunity is another area of uncertainty. Studies of seasonal cold-causing coronaviruses indicate that immunity is [relatively short lived](#) (lasting around 6 months to a year). However, follow-up of recipients of available vaccines so far indicates [good maintenance](#) of virus-specific immune responses.

An important question is whether vaccination can prevent asymptomatic SARS-CoV-2 infection and onward transmission; so far, the results released from efficacy trials focus primarily on prevention of symptomatic COVID-19. Dr. Monica Gandhi is maintaining a [table of available data](#) via twitter, which so far appears promising.

The Leading Vaccines

The table below summarizes information on leading vaccines but is not exhaustive (the [New York Times vaccine tracker](#) has more comprehensive information on the panoply of current products). Efficacy against symptomatic COVID-19 has varied somewhat, but prevention of severe disease, hospitalization and death has appeared consistent with all vaccines. While it's sometimes reported that efficacy against severe outcomes is "100%," this is [not necessarily proven](#) because these endpoints were relatively scarce in clinical trials.

Safety profiles have generally been favorable, with the major reported side effects typical of vaccines: injection site pain, muscle soreness, headache and fatigue. The Moderna and Pfizer/BioNTech mRNA vaccines can very rarely cause allergic reactions, which need to be monitored for immediately after immunization. The most serious concern to have emerged relates to [rare cases of unusual and potentially fatal blood clotting disorders](#) after immunization with the AstraZeneca vaccine; investigations are underway and there are disagreements in the scientific and regulatory communities regarding the causative role of the vaccine and whether usage should be restricted for younger age groups who are at lower risk for severe COVID-19 outcomes. The AstraZeneca vaccine has not yet been approved for use in the United States.

Initial efficacy trials involved adults, but vaccine developers have since expanded testing to children and adolescents, with promising results [just reported](#) for the Pfizer/BioNTech vaccine. A small number of pregnancies occurred in efficacy trials without evidence of untoward effects, and several specific studies for pregnant women are now enrolling.

Manufacturer	Name/type of vaccine	# of doses	# of recipients in efficacy trials	Efficacy against mild disease	Protection against severe disease
Pfizer/ BioNTech	BNT162b2 (tozinameran) mRNA	2	~22,000	95% ¹	9 cases in placebo arm, 1 case in vaccine
Moderna	mRNA-1273 mRNA	2	~15,000	94.1% ²	30 cases in placebo arm, 0 in vaccine arm ^{Error! Bookmark not defined.}
AstraZeneca	ChAdOx1, AZD1222, Covishield (in India) Chimpanzee adenovirus vector	2	~40,000	Initial studies: 62.1% (2 standard doses), 90.0% (low dose followed by standard dose), 70.4% (overall) ^{3,4} No efficacy against mild/moderate disease in South Africa ⁵ US phase III trial: 76% ⁶	10 cases in placebo arm, 0 cases in vaccine arm US phase III trial: 8 cases in placebo arm, 0 cases in placebo arm
Johnson & Johnson	Ad26.COVS.2.S Adenovirus serotype 26 (Ad26) vector	1	~22,000	72% in United States, 66% in Latin America, 57% in South Africa ⁷	85% (across United States, Latin America & South Africa)
Gamaleya National Research Centre for Epidemiology and Microbiology	Gam-COVID-Vac (Sputnik V) Adenovirus Ad26 and Ad5 vectors	2	~16,000	91.6% ⁸	20 cases in placebo arm, 0 in vaccine arm
Sinovac Biotech Ltd.	CoronaVac Whole-killed vaccine	2	~7,000	50.65% for all cases, 83.70% for cases requiring medical treatment (Brazil), 91.25% all cases (Turkey) ⁹	N/A
Novavax	NVX-CoV2373 Recombinant protein + Matrix M adjuvant	2	~9700	89.3% in UK, 60% in South Africa (HIV-participants) ^{10,11}	2 cases in placebo arms, 0 cases in vaccine arms

¹ <https://www.nejm.org/doi/full/10.1056/NEJMoa2034577>

² <https://www.nejm.org/doi/full/10.1056/NEJMoa2035389>

³ [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)32661-1/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32661-1/fulltext)

⁴ https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3777268

⁵ <https://www.statnews.com/2021/02/07/south-africa-halts-rollout-of-astrazenecas-covid-19-vaccine-after-shot-falters-against-variant/>

⁶ <https://www.astrazeneca.com/content/astraz/media-centre/press-releases/2021/azd1222-us-phase-iii-primary-analysis-confirms-safety-and-efficacy.html>

⁷ <https://www.jnj.com/johnson-johnson-announces-single-shot-janssen-covid-19-vaccine-candidate-met-primary-endpoints-in-interim-analysis-of-its-phase-3-ensemble-trial>

⁸ [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(21\)00234-8/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00234-8/fulltext)

⁹ http://www.sinovac.com/?optionid=754&auto_id=922

¹⁰ <https://ir.novavax.com/news-releases/news-release-details/novavax-covid-19-vaccine-demonstrates-893-efficacy-uk-phase-3>

¹¹ In an analysis including 148 participants living with HIV, efficacy diminished to 49.4%. Further details and potential explanations for lack of evidence of efficacy in the HIV+ cohort are not yet available.

Making a Vaccine Available

The Our World in Data website is [tracking global rollout](#) of COVID-19 vaccines.

Multiple efforts are underway to facilitate large-scale production, including unprecedented collaborations between vaccine manufacturers and other pharmaceutical companies with production capacity. There is a lack of transparency on pricing, which can vary depending on the purchasing entity, but [compilations of available data](#) show a range from \$2.15 to \$37 per dose for the available products. The [Serum Institute of India](#) has [an agreement](#) with Gavi and the Bill & Melinda Foundation to produce both the Oxford/AstraZeneca and Novavax vaccines at a maximum price of US\$3 per dose for low and middle-income countries.

The WHO, in partnership with the CEPI and Gavi, has formed [the COVAX facility](#), with the goal of providing access for the highest risk populations globally. Currently, however, COVID-19 vaccine distribution is mirroring the inequities that occurred when combination antiretroviral therapy for HIV first became available, with millions of vaccinations occurring in resource-rich countries and a relative paucity in the global south.

A coalition of over 140 global leaders, experts, elders and advocates have [issued a call](#) for a “people’s vaccine” and requested guarantees that COVID-19 vaccines, diagnostics, tests and treatments are “provided free of charge to everyone, everywhere.” The [People’s Vaccine Alliance](#) noted that, as of February 4, 2021, a total of 108 million COVID-19 vaccine doses have been given across 67 countries but [only 4.4% were in developing countries](#). The alliance is demanding suspension of intellectual property rules, sharing of technology and ending of monopolies in an effort to accelerate the equitable distribution of COVID-19 vaccines.

The African Union issued a [strong statement](#) emphasizing the “urgent need for countries to make full use of legal and policy measures, including flexibilities enshrined under the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) and Doha Declaration, South-South and North-South collaboration to ensure monopolies do not stand in the way of access to COVID-19 vaccines.”

Community Participation

Community involvement in vaccine research is well established for HIV and a growing part of the research effort for other diseases. It is vital that there is broad stakeholder input into the range of issues that affect the development and rollout of COVID-19 vaccines—including efficacy testing, safety, practicality, effectiveness across different populations, cost and global access. Stakeholders must include the communities most heavily impacted by the disease and civil society activists with experience in issues of vaccine research and

development. TAG have joined with [AVAC](#) and the [International Treatment Preparedness Coalition](#) (ITPC) to form the [COVID Advocates Advisory Board](#) (CAAB), see the website for more information.