

COVID-19

Vaccine Efficacy and Real-World Effectiveness Overview

DECEMBER 2021



ABOUT ITPC

The International Treatment Preparedness Coalition (ITPC) is a worldwide network of community activists unified by our vision of a longer, healthier, more productive life for all people living with HIV (PLHIV). ITPC's mission is to enable communities in need to access optimal HIV treatment. As a grassroots movement based primarily in the Global South, ITPC is the community's voice on HIV treatment and is driven by and committed to the human rights of those most impacted by the HIV epidemic.

ITPC is a global coalition that includes eight regional networks in Africa, Asia, Latin America and the Caribbean, Eastern Europe, and the Middle East. Through its different campaigns, ITPC is committed to providing accurate and timely HIV treatment information that can improve the lives of PLHIV. Many of the tools developed under this program are also intended to be used for advocacy initiatives.

Additional information about ITPC is available at: www.itpcglobal.org.

ACKNOWLEDGMENTS

Dedicated to all of the people who lost their lives to COVID-19 and their families and friends.

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ABBREVIATIONS

APC Antigen-presenting cell (s)

CDC Centers for Disease Control

COVID-19 Coronavirus Disease 2019

EMA European Medicines Agency

EUL Emergency Use Listing

FDA Food and Drug Administration

mRNA messenger RNA

PLHIV people living with HIV

SARS-CoV-2 Severe Acute Respiratory Syndrome Coronavirus-2

TTS thrombosis with thrombocytopenia syndrome

UK United Kingdom

US United States

US FDA United States Food and Drug Administration

WHO World Health Organization

Covid-19 Vaccine Efficacy and Real-World Effectiveness Overview

Background

By November 2021, globally, more than five million deaths were officially attributed to COVID-19, the illness caused by the SARS-CoV-2 virus. The *Economist* estimates the actual death toll at close to 20 million, based on excess mortality rates during the global pandemic.¹

Although large gaps in our knowledge of SARS-CoV-2 remain, the rapid development of COVID-19 vaccines is an ongoing and remarkable scientific response to the global pandemic. These vaccines, which use different platforms to generate immune responses to SARS-CoV-2, have proven safe and effective in clinical trials, and are being rolled out across the world – albeit inequitably – on an emergency basis. Nonetheless, billions of people have become de facto participants in testing safety, effectiveness, and durability of these vaccines in the real world.

In this overview, we summarize two sets of currently available data: from randomized, placebo controlled, Phase III clinical trials that provide baseline efficacy estimates, and observational studies estimating real-world effectiveness after vaccine roll-out.

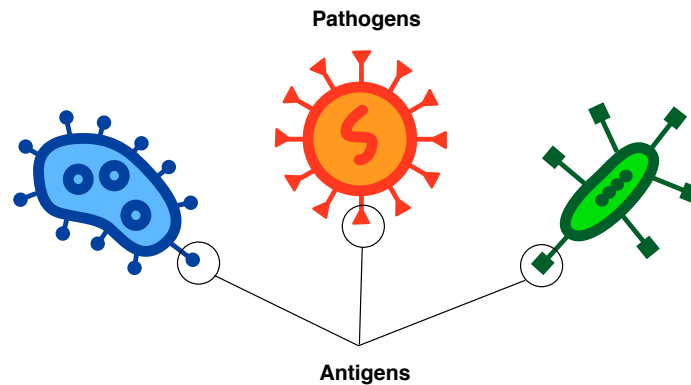
There are hundreds of vaccine candidates in various stages of development world-wide. Here, we focus on vaccines included (and submitted: Sputnik V) in the World Health Organization (WHO) Emergency Use Listing (EUL)² as of November 2021:

- Pfizer-BioNTech (BNT162b2, Comirnaty);
- Moderna (mRNA-1273, SpikeVax);
- AstraZeneca-Oxford (ChAdOx1, AZD1222, Vaxzervia/Covidshield);
- Johnson and Johnson-Janssen (Ad26.COVS.2.S);
- Bharat Biotech (BBV152, Covaxin);
- Gamaleya (Gam-COVID-Vac, Sputnik V);
- Sinovac (CoronaVac); and
- Sinopharm (BBIBP-CorV/VeroCell).

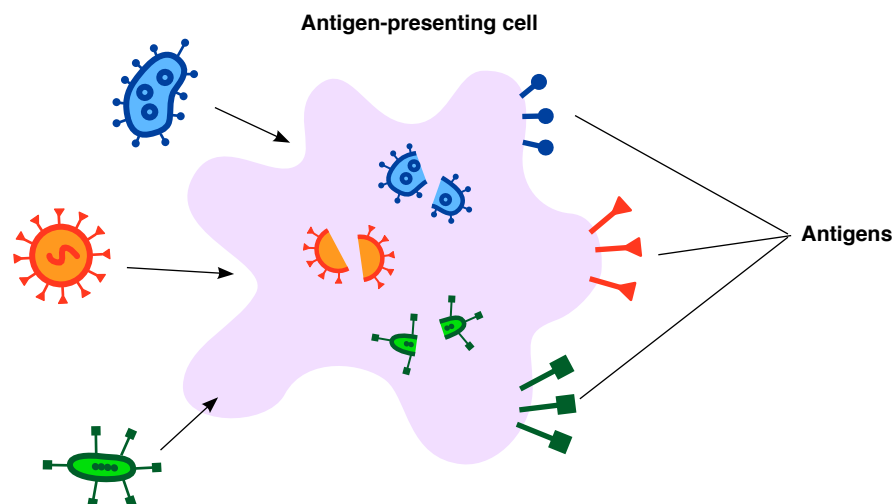
We have provided explanations of immune responses and how vaccines using different platforms trigger these responses.

The Immune System

The immune system works in different ways to keep us healthy. Innate immunity is the body's first line of defense against toxins, viruses and other disease-causing microorganisms (called *pathogens*). Innate immune responses are non-specific; they aim to stop all pathogens from spreading into the body. Some pathogens can escape these immune responses – which is when adaptive immune responses work to prevent them from causing illness.



The adaptive immune response is pathogen specific. Each pathogen has unique markings on its surface, called *antigens*; these trigger specific immune responses from *antigen-presenting cells (APC)*, *T cells* and *B cells*.



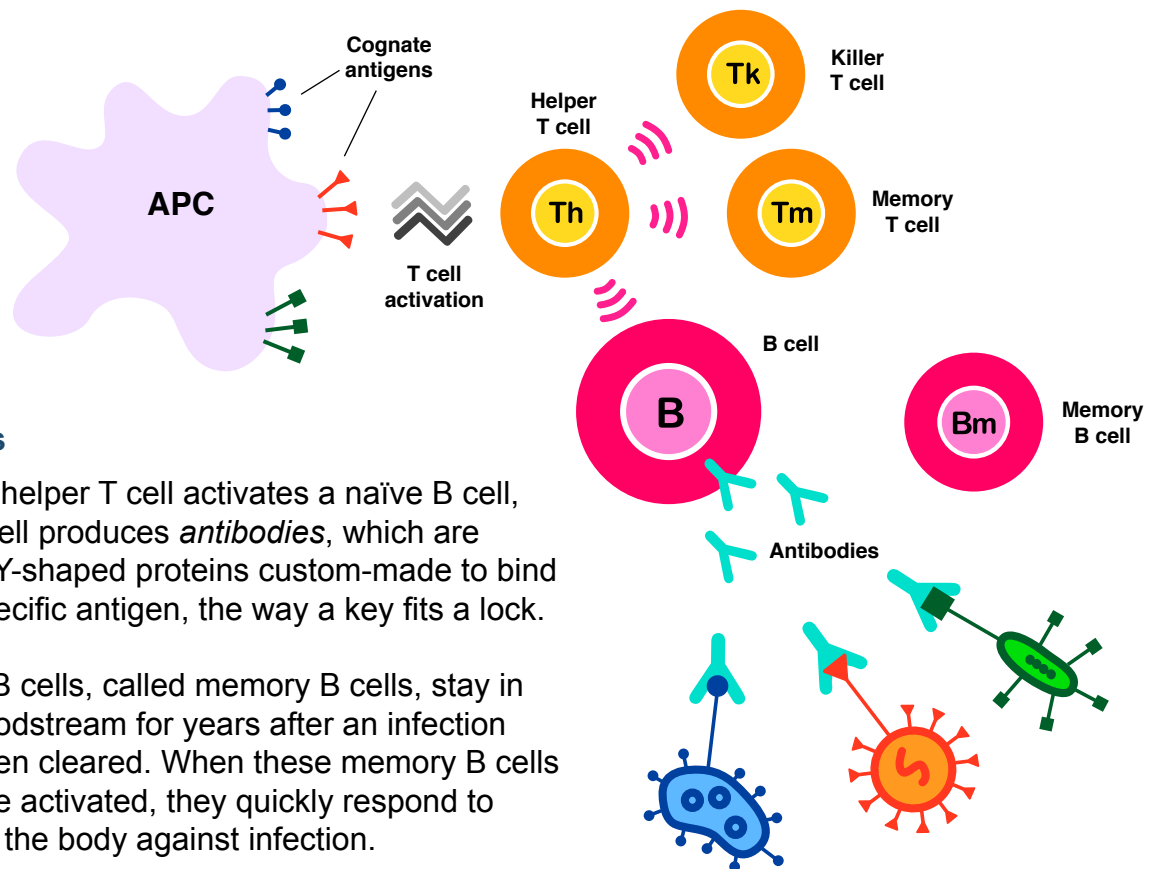
Antigen-Presenting Cells

APC are part of innate and adaptive immune responses. They patrol the bloodstream, looking for invaders. When APCs recognize an antigen, they swallow the entire pathogen, chop it into pieces and display these pieces on their surface where T cells and B cells can see them.

T Cells

Helper T cells, killer T cells, and memory T cells are part of the adaptive immune system. They work together to prevent pathogens from causing illness. Helper T cells become activated when they recognize a specific antigen (called a *cognate antigen*) displayed by an APC.

Once they are activated, helper T cells coordinate the immune response by signaling other immune system cells, including killer T cells (which destroy infected cells), memory T cells (which remember and rapidly respond to their cognate antigen for many years), and B cells (which produce antibodies or become memory B cells).



B Cells

After a helper T cell activates a naïve B cell, the B cell produces *antibodies*, which are sticky, Y-shaped proteins custom-made to bind to a specific antigen, the way a key fits a lock.

Some B cells, called memory B cells, stay in the bloodstream for years after an infection has been cleared. When these memory B cells become activated, they quickly respond to defend the body against infection.

Antibodies

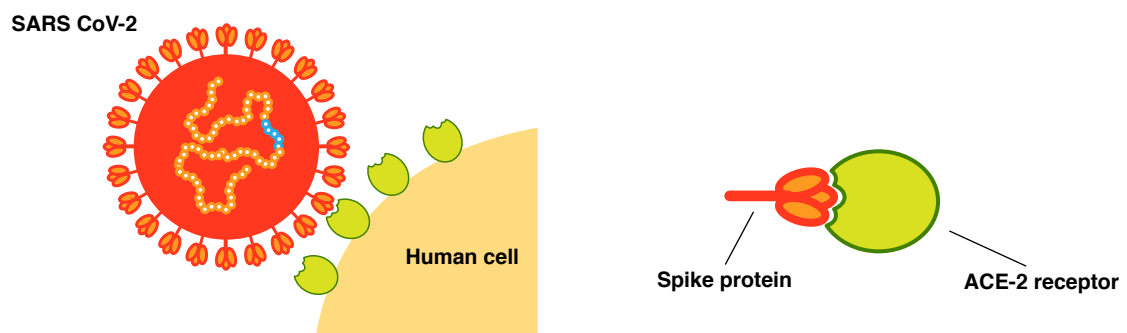
Neutralizing antibodies prevent illness by stopping pathogens, including SARS-CoV-2, from entering cells. Other antibodies protect people from falling ill by disabling pathogens, or marking pathogens and infected cells for destruction by killer T cells.

Antibody levels (called *titers*) typically diminish over time, but cellular immune responses to COVID-19 vaccines (memory T cells and memory B cells) are long-lived and will respond rapidly if they encounter SARS-CoV-2.

Vaccine Targets

Vaccines work by preparing the immune system to fight off specific pathogens, usually by showing harmless versions or parts of the pathogen to the immune system. They need a good target – for example, part of a virus that is unlikely to change much – to trigger immune responses.

SARS-CoV-2 vaccines use the virus's *spike protein* as their target. The spike protein enters cells that are found throughout the body, fitting into a protein on their surface called the ACE-2 receptor as a key fits into a lock. These vaccines prepare the immune system to recognize the spike protein and make antibodies that can prevent it from entering cells and trigger the immune system to kill off infected cells.



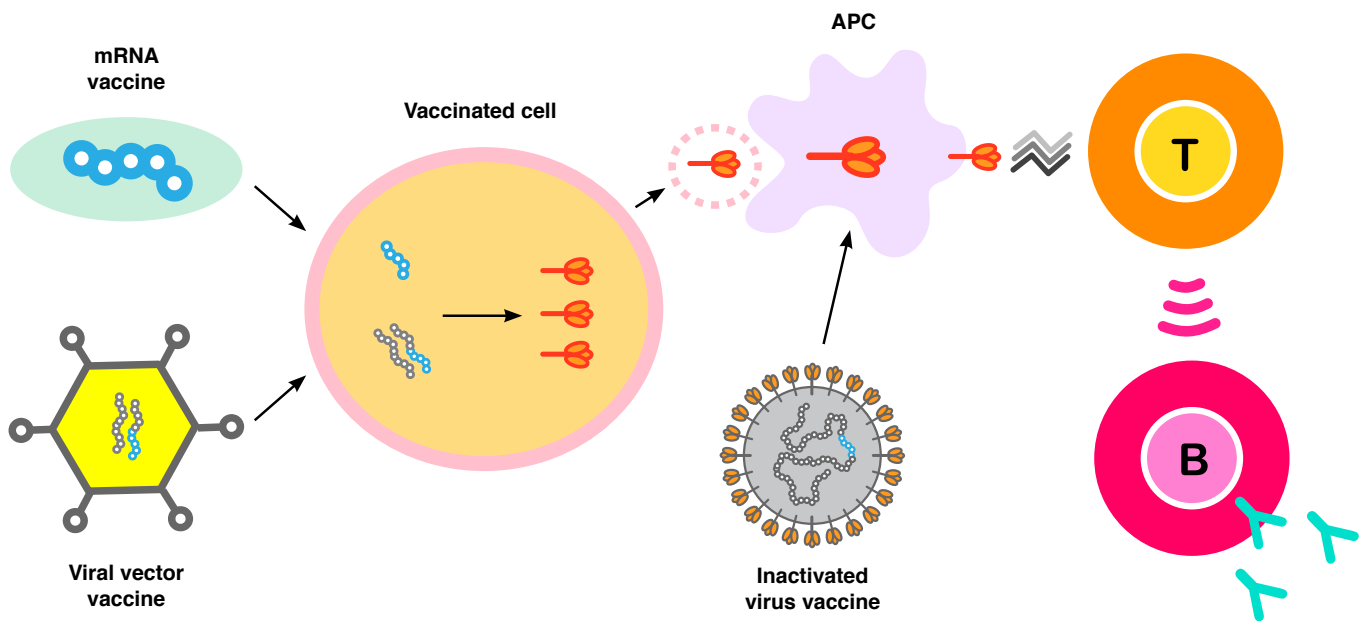
How COVID-19 Vaccines Work

These vaccines use different approaches to do the same thing: trigger immune responses to SARS-CoV-2. Some of these vaccines, called inactivated viral vaccines, use harmless versions of SARS-CoV-2, or parts of the virus, to elicit immune responses without making a person ill with COVID-19. Other vaccines, called mRNA vaccines, provide instructions for making SARS-CoV-2 spike proteins, instead of using the actual virus or parts of it, to elicit antibody production and other immune responses. Viral vector vaccines use an inactivated virus as an envelope to deliver spike protein-making DNA into cells. These spikes trigger immune responses to SARS-CoV-2.

mRNA Vaccines

The Moderna and Pfizer/BioNTech vaccines are mRNA-based. The technology used to create them has been in development for decades. The mRNA-based COVID-19 vaccines are the first using this platform to reach the market.

These vaccines use synthetic *messenger RNA (mRNA)* to instruct cells to build proteins – in this case, only the spike protein, without the rest of the SARS-CoV-2 virus. The mRNA is wrapped in fat bubbles (called *lipid nanoparticles*) that protect their contents until they enter cells. Then, lipid nanoparticles meld into cells and deliver the recipe for making spike proteins. After vaccinated cells build spike proteins, they die – and some of the spikes – or pieces of them – poke out from their surface, attracting antigen-presenting cells, which display these spikes to the immune system, eliciting immune responses.



Viral Vector Vaccines

The Gamaleya, Johnson and Johnson (J & J) and Oxford/AstraZeneca COVID-19 vaccines are viral vector-based vaccines. They use *inactivated cold viruses*, called adenoviruses, which are modified to enter, but not infect cells. These adenoviruses deliver spike protein-making instructions into cells, and stimulate the immune system. Gamaleya’s vaccine, Sputnik V, uses two different adenoviruses for additional immune stimulation; the J & J and Oxford/AstraZeneca vaccines use a single adenovirus.



After entering cells, adenoviruses deliver spike protein DNA directly into the cell’s control center, the nucleus, where it is converted into mRNA. Then, cells use the mRNA to build spike proteins. Some of these spikes – or pieces of them – poke out from the surface of vaccinated cells, which die. Antigen-presenting cells sweep up the spikes and display them to elicit immune responses.

Inactivated Virus Vaccines

The Bharat Biotech, Sinopharm and Sinovac vaccines are based on inactivated viruses. They use harmless versions of SARS-CoV-2, treated with heat, radiation, or chemicals so they cannot replicate or cause illness, although their proteins are intact. These inactivated viruses are mixed with an immune stimulant called an adjuvant, to enhance immune responses. After vaccination, antigen-presenting cells sweep up the inactivated viruses and present them to T cells and B cells, triggering immune responses to the spike protein.



About SARS-CoV-2 Variants

Viruses must enter host cells to reproduce. Once they do, they will make millions to billions of copies of themselves each day. Some of these copies have errors or changes, called mutations; they are different from the original virus. Mutations can weaken viruses or make them more contagious, and/or able to cause more severe disease, and/or change the effectiveness of vaccines, treatments, and diagnostics.

A group of viruses that share mutations is called a variant. The World Health Organization (WHO), in collaboration with a multinational group of experts, has been monitoring changes to, and variants of SARS-CoV-2. These variants are categorized as:

Variants Under Monitoring, which have genetic changes that are suspected to affect virus characteristics, with some indication that it may pose a future risk, but evidence of phenotypic or epidemiological impact is currently unclear, requiring enhanced monitoring and repeat assessment pending new evidence.

Variants of Interest, which have genetic changes that are predicted or known to affect virus characteristics such as transmissibility, disease severity, immune escape, diagnostic or therapeutic escape; AND identified to cause significant community transmission or multiple COVID-19 clusters, in multiple countries with increasing relative prevalence alongside an increasing number of cases over time, or other apparent epidemiological impacts to suggest an emerging risk to global public health.

Variants of Concern (currently Alpha, Beta, Gamma, Delta, and Omicron) are associated with one or more of the following changes at a degree of global public health significance:

- Increase in transmissibility or detrimental change in COVID-19 epidemiology; OR
- Increase in virulence or change in clinical disease presentation; OR
- Decrease in effectiveness of public health and social measures or available diagnostics, vaccines, therapeutics.³

How Vaccine Efficacy Was Determined in Clinical Trials, and What Does it Mean for COVID-19 Vaccines?

“...We should expect SARS-CoV-2 vaccines to prevent disease, but without a transmission-blocking vaccine or achieving herd immunity, we cannot expect to vaccinate our way back to 100% of our pre-pandemic activities.”⁴

After an experimental vaccine has demonstrated safety in smaller Phase I trials, which include laboratory testing of immune responses, it moves on to Phase II trials. If still safe and showing efficacy, the vaccine can advance to larger Phase III clinical trials, which are usually the basis for regulatory approval.

Efficacy Versus Effectiveness

Efficacy is a term used to describe how well a vaccine can prevent illness – and possibly transmission – under specific conditions, such as in placebo-controlled clinical trials.

Effectiveness describes how well a vaccine works in real-world circumstances.

Randomized, placebo-controlled Phase III vaccine trials are designed to rule out the possibility that results happened by chance or were influenced by the placebo effect and/or other factors. In the Phase III COVID-19 vaccine trials, thousands of study volunteers were selected at random to receive the vaccine or placebo. The vaccine’s efficacy at preventing infection with, or illness from SARS-CoV-2 was determined by comparing the number of people who got COVID-19 in each group within a specific timeframe. The larger the difference between the groups, the higher the vaccine’s efficacy – which was reported as a percentage.

Counting SARS-CoV-2 infections in a large trial requires frequent testing, since many infected people are asymptomatic and can clear the infection quickly. Most of the randomized, controlled COVID-19 vaccine trials relied on self-reported COVID-19 symptoms (e.g., fever, cough, shortness of breath) to trigger SARS-CoV-2 testing. It is very likely that asymptomatic SARS-CoV-2 infections during vaccine trials among both vaccine and placebo recipients were undetected and unreported.

Challenges for Future COVID-19 Vaccine Trials

Identifying specific immune responses that are predictive of protection against COVID-19 has become increasingly important for future vaccine development. Numerous studies have linked higher titers of neutralizing antibodies with population-level protection against symptomatic COVID-19.

Other types of immune responses also play a role in preventing infection with, and illness from SARS-CoV-2.

So far, correlates of protection at the individual level have not been characterized – in other words, the individual threshold over which COVID-19 vaccines are effective is not currently known. This information will facilitate and accelerate vaccine research.

Now that safe and effective vaccines have been approved by regulatory authorities, placebo-controlled COVID-19 vaccine trials are no longer ethical. Comparing infection rates between study participants who got placebo or different vaccines is time-consuming and costly, and results are subject to epidemiological, viral, host, behavioral and other factors. If correlates of protection are identified, trials could be done less expensively and more quickly, speeding access to new vaccines.⁵

What Does This Mean?

Preventing SARS-CoV-2 Infection

It is common sense that people with some immunity to a virus are less likely to become infected or re-infected with it than people without any immunity – and, following this logic, that people who do not have a virus cannot transmit it. In fact, available evidence from clinical trials and observational studies suggests that fully vaccinated people are less likely to become infected with SARS-CoV-2 than unvaccinated persons, although if they become infected, they can still transmit the virus to other people (including the fully vaccinated).⁶ Other factors, such as community vaccination and infection rates, the infectiousness of circulating viral variants, and adherence to masking and other preventive measures play a role in transmission rates.

Currently approved intramuscular vaccines are better at generating immune responses in the lower respiratory tract than in the upper respiratory tract sites where SARS-CoV-2 enters the body. This means that vaccines are highly effective against the consequences of SARS-CoV-2 infection: severe illness, hospitalization and death – and perhaps, long COVID – but less effective at blocking infection.

Preventing Severe Illness, Hospitalization and Death from COVID-19

Generally, antiviral vaccines are considered highly effective if they can trigger immune responses in early infection that reduce viral load (and transmission risk) and, more importantly, can clear the infection before it progresses to serious disease.⁷

When a sufficient number of trial volunteers have developed severe COVID-19 and/or are hospitalized, a vaccine's efficacy against these outcomes can be estimated. Most clinical trials of COVID-19 vaccines did not follow people for enough time (e.g., only two months) to provide accurate estimates of vaccine efficacy against death from COVID-19, or to inform us about the durability of protection.

Study Populations

For safety and ethical reasons, most volunteers in early-stage COVID-19 vaccine trials were younger and healthier than the general population. Some Phase III trials enrolled older people (>65 years) and people with pre-existing conditions known to worsen COVID-19, such as diabetes, HIV, hypertension and obesity, but not in large enough numbers to generate information about vaccine efficacy in these groups. People who were pregnant or immunocompromised, including solid organ transplant recipients and people undergoing chemotherapy, were not eligible to participate in Phase III trials. Currently, trials are looking at the safety and efficacy of, and side effects from approved COVID-19 vaccines among people with different cancers, transplant recipients, people with autoimmune and inflammatory diseases, people living with HIV and dialysis recipients (for more information, see www.clinicaltrials.gov).

Limitations of Data from Clinical Trials

These trials usually followed people for a short period of time, so their results do not shed light on the durability of protection from vaccines; we need to rely on observational studies for this information.

The Phase III clinical trials of currently authorized and approved vaccines should be seen in their historical context, before more transmissible variants, such as Delta, became globally dominant. Real-world Delta-era data are just becoming available from observational studies.

It is not possible to compare the efficacy of different vaccines, because COVID-19 vaccine trials were not standardized; their testing triggers, methods and schedules differed, as did outcome measurements (such as the definition of severe COVID-19 or when hospitalization was necessary). In addition, most Phase III trials were conducted during 2020 and early 2021, in different countries – where different SARS-CoV-2 variants were circulating – and among different populations, such as healthcare workers, who were at higher risk for infection than the general population.

Keeping these caveats in mind, Table 1 is a summary of vaccine efficacy from clinical trials.

Table 1: COVID-19 Vaccine Efficacy from Phase III Randomized, Controlled Trials

Vaccine Producer and Name	Platform	Dosing	Trial size	Protection Against Symptomatic Infection	Protection Against Severe Disease/ Hospitalization
Pfizer-BioNTech (BNT162b2, Comirnaty) ⁸	mRNA	2-dose 3 weeks apart	43,548	95%	100%
Moderna (mRNA-1273, SpikeVax) ⁹	mRNA	2-dose 4 weeks apart	30,420	94%	100%
AstraZeneca-Oxford (ChAdOx1, AZD1222, Vaxzervia, Covidshield) ¹⁰	Viral Vector	2-dose 4 weeks apart	32,451	74%	100%
Johnson & Johnson-Janssen (Ad26.COV2.S) ¹¹	Viral Vector	1 dose	43,448	66%	85%
Gamaleya (Sputnik V, Gam-COVID-Vac) ¹²	Viral Vector	2-dose 3 weeks apart	21,997	92%	N/A
Bharat Biotech (BBV152, Covaxin) ¹³	Viral Vector	2-dose 4 weeks apart	25,798	78%	93%
Sinovac (CoronaVac) ¹⁴	Inactivated Virus	2-dose 2 weeks apart	10,218	84%	100%
Sinopharm (BBIBP-CorV, VeroCell) ¹⁵	Inactivated Virus	2-dose 3 weeks apart	45,000	78%	79%

Observational Studies of COVID-19 Vaccine Effectiveness

Observational studies have followed outcomes among unvaccinated, partially vaccinated and fully vaccinated people (defined as: two weeks after receiving the second dose of a two-dose series, or two weeks after a single-dose vaccine).

These studies were mainly done in high-income countries, limiting information to vaccines from J & J, Moderna, AstraZeneca/Oxford and Pfizer/BioNTech – and they are not direct, head-to-head comparisons.

Partial versus Full Vaccination for COVID-19

An analysis of data from Public Health England found that getting both doses of the AstraZeneca/Oxford or Pfizer/BioNTech COVID-19 vaccine was much more effective against the Delta variant than a single dose of either vaccine. Single doses of the Oxford/AstraZeneca and Pfizer/BioNTech vaccine were 30% and 36% effective for preventing symptomatic COVID-19, respectively, with effectiveness increasing to 67% and 87%, respectively, after a second dose.¹⁶

Using observational data to assess the effectiveness of COVID-19 vaccines is complicated, because of changes in the background context, such as:

- Shifts in the epidemic
- Emergence of new viral variants, some of which may be more infectious and/or better able to evade immune responses
- Evolution of national and/or local preventive measures
- Changes in individual behaviors such as masking and social distancing
- Waning of vaccine-induced protection over time
- Number of people who have some degree of immunity from SARS-CoV-2 infection (and waning of this protection)
- Changes in vaccine scheduling, which may increase or decrease their effectiveness
- Vaccine mixing, which may impact vaccine effectiveness
- Asymptomatic infections: since people are not tested, they are not counted or reported
- Reluctance to get tested when it leads to loss of income or other consequences

Observational trials can partially, but not fully, account for some of these variables by study design (prospective and retrospective cohorts, test-negative case control, etc.) and by controlling for these factors during analysis.

Vaccine effectiveness in a test negative study is estimated by comparing outcomes between vaccinated vs. unvaccinated people with COVID-19-like symptoms who have access to, and seek medical care. While people who are more likely to get vaccinated are also more likely to get tested and to access care than unvaccinated people, these studies can reduce this potential bias by looking only at more serious outcomes such as hospitalization and ICU admission, when healthcare-seeking behaviors are thought to be more equivalent. The results from test negative studies are usually not generalizable outside of the community settings where data were collected, and are unlikely to provide information on underserved and marginalized populations with limited access to care.¹⁷

Currently available data are limited, especially for the Delta variant, since the most recent published data were collected and analyzed up to September 2021. Most of the vaccine effectiveness data are based on a relatively small number of people who become severely ill. It is especially challenging to estimate vaccine effectiveness based on severe illness, hospitalization and death in younger people, since they are at lower risk for these outcomes.

Vaccine Effectiveness Against Infection, Serious Illness, Hospitalization, Death

The number of breakthrough infections among fully vaccinated people will increase as they make up a greater proportion of the population, although fully vaccinated people are less likely to become infected than unvaccinated people. Although vaccine-induced protection against infection may wane over time, vaccines also prepare the immune system to better fight off infection before people become seriously ill, hospitalized with, or die from COVID-19.

In the United States (US), after the Delta variant became dominant in June 2021, The Centers for Disease Control (CDC) reported that fully vaccinated people were five times less likely to become infected with SARS-CoV-2, and 10 times less likely to be hospitalized or die from it than unvaccinated people.¹⁸ In the United Kingdom (UK), the Office for National Statistics followed COVID-19 deaths between 2 January 2021 and 2 July 2021. It reported 51,281 COVID-19 deaths; only 640 of them occurred among fully vaccinated people (many of whom were over 80 years of age and/or immunocompromised).¹⁹ In Texas, the Department of State Health Services reported that during the period from 4 September to 1 October 2021, unvaccinated people were 13 times more likely to become infected with SARS-CoV-2, and 20 times more likely to die from it than fully vaccinated people.²⁰

How Well do These Vaccines Work?

This report focused on studies that provided effectiveness estimates for specific vaccines. Table 2 includes peer-reviewed, published studies and reports from the CDC and Public Health England. No observational data on Bharat Biotech's Covaxin were available as of mid-November 2021.

Table 2: COVID-19 Vaccine Effectiveness from Observational Studies

Vaccine	Study Location, Method, Total Size	Time Frame/ Variant (s) in Circulation	Population (s)	Any Infection	Symptomatic Disease	Hospitalization	Death
Pfizer-BioNTech (BNT162b2, Comirnaty)	USA; Test negative ²¹ Size: 63,104	Jan-Jun 2021/ Alpha dominant	Age ≥ 50		89%	87%	
	USA; Retrospective cohort, up to 6 months post-vaccination ²² Size: 3,436,957	Dec 2020-Aug 2021/ All variants, including Delta	Age ≥ 16	72%		90%	
			Age ≥ 65	61%		86%	
	USA 9 States; Test negative ²³ Size: 32,867	Jun-Aug 2021/ Delta dominant	Age ≥ 18		77%	80%	
	USA 9 States; Test negative ²⁴ Size: 89,217	Jan-Sep 2021 All variants, including Delta	Age ≥ 18, Immunocompromised; > 2 weeks post vax			71%	
	USA 18 States; Test negative ²⁵ Size: 3,689	Mar-Aug 2021 All variants, including Delta	Age ≥ 18; Non-immunocompromised; > 2 weeks post vax			91%	
			Age ≥ 18; Non-immunocompromised; 3 months post vax			77%	
	UK; Test negative ²⁶ Size: 4,737,939	Dec 2020 – Sep 2021 Alpha and Delta dominant	Age ≥ 16; 2-9 weeks post vax		90%	98%	98%
			Age ≥ 16; 20+ weeks post vax		70%	93%	90%
			Age ≥ 65; 2-9 weeks post vax		80%	98%	97%
			Age ≥ 65; 20+ weeks post vax		55%	91%	91%
Hungary, Retrospective cohort ²⁷ Size: 3,740,066	Jan-Jun 2021 Alpha dominant	Age ≥ 16	83%			91%	
Moderna (mRNA-1273, SpikeVax)	USA, Test negative ²¹ Size: 63,104	Jan-Jun 2021 Alpha dominant	Age ≥ 50		92%	91%	
	USA 9 States, Test negative ²³ Size: 32,867	Jun-Aug 2021 Delta dominant	Age ≥ 18		92%	95%	
	USA 9 States, Test negative ²⁴ Size: 89,217	Jan-Sep 2021 All variants, including Delta	Age ≥ 18 Immunocompromised; > 2 weeks post vax			81%	
	USA 18 States, Test negative ²⁵ Size: 3,689	Mar-Aug 2021 All variants, including Delta	Age ≥ 18; Non-immunocompromised; 2 weeks post vax			93%	
			Age ≥ 18; Non-immunocompromised; 3 months post vax			92%	
	Hungary, Retrospective cohort ²⁷ Size: 3,740,066	Jan-Jun 2021 Alpha dominant	Age ≥ 16	89%			94%

Vaccine	Study Location, Method, Total Size	Time Frame/ Variant (s) in Circulation	Population (s)	Any Infection	Symptomatic Disease	Hospitalization	Death
Johnson & Johnson-Janssen (Ad26. COV2.S)	USA, Test negative ²¹ Size: 63,104	Jan-Jun 2021 Alpha dominant	Age ≥ 50		73%	68%	
	USA 9 States; Test negative ²³ Size: 32,867	Jun-Aug 2021 Delta dominant	Age ≥ 18		65%	60%	
	USA 18 States; Test negative ²⁵ Size: 3,689	Mar-Aug 2021 All variants, including Delta	Age ≥ 18; Non-immunocompromised; 1 month post vax			68%	
	USA 5 states; Retrospective Cohort ²⁸ Size: 97,787	Feb-Jul 2021	Age ≥ 18	74%			
AstraZeneca-Oxford (ChAdOx1, AZD1222, Vaxzervia, Covidshield)	Brazil; Test negative ²⁹ Size: 61,164	Jan-Jul 2021 Gamma dominant	Age ≥ 60; single dose; 1 month post vax		33%	55%	62%
			Age ≥ 60; 2 doses; 3 months apart		78%	88%	94%
	UK; Test negative ²⁶ Size: 4,732,939	Dec 2020 - Sep 2021 Delta dominant	Age ≥ 16; 2-9 weeks post vax		67%	95%	94%
			Age ≥ 16; 20+ weeks post vax		47%	77%	79%
			Age ≥ 65; 2-9 weeks post vax		59%	92%	93%
			Age ≥ 65; 20+ weeks post vax		37%	76%	79%
	Hungary; Retrospective cohort ²⁷ Size: 3,740,066	Jan-Jun 2021 Alpha dominant	Age ≥ 16	72%			88%
Sinovac (CoronaVac)	Chile; Prospective cohort ³⁰ Size: 10,187,720	Feb-May 2021 Alpha + Gamma dominant	Age ≥ 16		66%	88%	86%
			Age ≥ 60:		67%	85%	87%
	Brazil; Test negative ³¹ Size: 43,774	Jan-Apr 2021 Gamma dominant	Age 70-74		59%	78%	84%
			Age 75-79		56%	67%	78%
			Age ≥ 80		33%	39%	44%
Sinopharm (BBIBP-CorV, VeroCell)	Hungary; Retrospective cohort ²⁷ Size: 3,740,066	Jan-Jun 2021 Alpha dominant	Age ≥ 16	69%			88%
Gamaleya (Sputnik V, Gam-COVID-Vac)	Hungary; Retrospective cohort ²⁷ Size: 3,740,066	Jan-Jun 2021 Alpha dominant	Age ≥ 16	86%			98%

Vaccine Safety and Side Effects

Minor reactions to COVID-19 vaccines that resolve within hours to days have been observed in clinical trials and vaccine rollout programs. They include injection site pain, swelling and redness, fever, fatigue, headaches, chills, and joint and muscle pain. These symptoms are normal, and caused by the immune response to the vaccine.

Phase III randomized, controlled trials were too small to capture very rare adverse events. Since the widespread rollout of vaccines, various post-vaccination adverse events have been reported, mainly from monitoring systems such as the US Vaccine Adverse Event Reporting System and EudraVigilance in the EU. When a specific adverse event is identified as happening more frequently with a certain vaccine, it must be actively investigated to determine if the vaccine caused it, or if it happened by coincidence.

Most data on adverse events are from high-income countries, since low- and middle-income countries do not always have the capacity for conducting surveillance on vaccine-related adverse events. There is no standardized international system for reporting and adjudicating adverse events; a globally coordinated system is urgently needed.³²

Serious Adverse Events

Serious but rare adverse events associated with COVID-19 vaccines have occurred.

Anaphylaxis

Rare, severe allergic reactions, called anaphylaxis, have been reported after receiving an mRNA-based COVID-19 vaccine. This reaction occurs within minutes to hours after vaccination.

In the US, 4.7 cases of anaphylaxis per million people were reported among recipients of the Pfizer/BioNTech vaccine, and 2.5 cases per million people among recipients of the Moderna vaccine. Most of them occurred in women and were treated with adrenaline. No deaths have been reported.³³

Heart inflammation (myocarditis and pericarditis)

Rare cases of heart inflammation have been reported, predominantly in men ages 12-29, after receiving the second dose of an mRNA vaccine. In the US, the overall rate of myocarditis/pericarditis among adult mRNA vaccine recipients was 3.5 cases per million, increasing to 24.3 cases per million among people ages 18-29. Most acute cases resolved after hospitalization. As of November 2021, 1,031 cases have been confirmed in the US, with no deaths.^{34,35}

In July 2021, The EMA updated product information for mRNA vaccines to include warnings after 145 cases of myocarditis and 138 cases of pericarditis occurred after vaccination with the Pfizer/BioNTech vaccine, and 19 cases of myocarditis and 19 cases of pericarditis occurred among recipients of the Moderna vaccine. Five deaths have been reported.^{36,37}

Notably, in Europe, as of May 2021, 34 cases of myocarditis and 47 cases of pericarditis have been reported after 40 million doses of the AstraZeneca/Oxford vaccine.³⁸ A causal relationship has not been determined.

Blood clotting with low platelets (Thrombosis with thrombocytopenia syndrome, or TTS):

In Europe, 100 cases of TTS, including ten deaths, were reported following 51.4 million doses of the AstraZeneca/Oxford vaccination as of June 2021. Worldwide, 1,503 cases have been reported as of July 2021. However, EMA noted the warning on increased risk to women under 60 has been removed after additional data and analysis did not show a large difference in TTS cases by sex.³⁹

TTS has been reported, mainly in females, under age 50 years who received the Johnson & Johnson vaccine. In the US, the reported rate of TTS was 3 per million, but 8.8 per million in females ages 30-49. As of November 2021, 50 reports of TTS were confirmed, with five deaths. Two confirmed cases, out of more than 409 million doses, have also been reported in people who got the Moderna mRNA vaccine.⁴⁰

Guillain-Barré syndrome (GBS)

Cases of this rare autoimmune neurologic disorder that can lead to paralysis have been reported, usually two weeks after receiving the Johnson & Johnson vaccine. In the US, the rate of GBS was 7.8 per million. It was higher among men ages 50-64, at 15.6 cases per million. As of June 2021, ten people have been admitted to the ICU, and one person has died. Worldwide, 108 cases have been assessed by the EMA as of June 2021 (after 21 million people received the Johnson & Johnson vaccine globally). There was one reported death.

In the EU, 227 cases of GBS were reported among recipients of the AstraZeneca/Oxford vaccine after 51.4 million doses of the vaccine were administered (as of June 2021). Globally, as of July 2021, 833 cases have been reported after 592 million vaccines were administered, but a causal relationship has not been confirmed to date.^{41,42}

COVID-19 Vaccine Effectiveness in Different Populations

Race and Gender

The higher death rate from COVID-19 among people of color is likely driven by structural racism and inequity – resulting in poor access to healthcare, living in crowded conditions, front-line work, and more comorbid health conditions. No difference in vaccine protection by race or ethnicity has been found in observational studies to date. Although men are at higher risk of severe COVID-19 than women, efficacy and real-world effectiveness studies have not found any gender-based differences in vaccine protection to date.

Children

In November 2021, the US CDC recommended that children ages 5-11 receive the Pfizer/BioNTech vaccine, based on a study showing 91% efficacy, similar to adults.⁴³ Moderna has submitted data to the US FDA, and is currently awaiting review.

Pregnancy

Pregnant people are at increased risk for severe illness and death from COVID-19, and for premature births. COVID-19 vaccines are safe, effective, and recommended during pregnancy. A large observational cohort study with pregnant people in Israel has been published, showing that full vaccination with the Pfizer/BioNTech vaccine among pregnant people was 97% effective against symptomatic infection and 89% effective against hospitalization, similar to the general population.⁴⁴

Immunocompromised People

A US-based study drawing from hospitalization records in nine states, estimated effectiveness of mRNA vaccines (Moderna and Pfizer/BioNTech) in immunocompromised people (including people with cancer, inflammatory disorders, organ/stem-cell transplant recipients, and other conditions). It found reduced effectiveness of 77% vs. 90% in immunocompetent people in similar settings.⁴⁵

Boosters

The debate over vaccine boosters – and who should receive them – has become a hot topic. It has pitted global vaccine equity and the need to stop SARS-CoV-2 variants from emerging against ensuring continued protection against severe illness and hospitalization with, or death from COVID-19 among vaccinated people in high-income countries.

Although vaccination does not always prevent SARS-CoV-2 infections, we can realistically expect that it will protect most people from severe illness with, and hospitalization and death from COVID-19.

There are three medical reasons for booster doses of COVID-19 vaccines, to address:

- Waning immunity (whether from an infection or vaccination) over time;
- Protection against new variants of SARS-CoV-2;
- Inadequate protection from vaccination, mainly among older and/or immunocompromised people (including people living with HIV, especially those who are untreated, and/or those with a high viral load and/or a low CD4 cell count).

Several studies have documented waning neutralizing antibody responses (although cellular immune responses are more persistent) - mainly to the Pfizer/BioNTech vaccine,⁴⁶ which has been studied extensively. It is difficult to link laboratory test results directly with real-world outcomes among vaccinated people, especially since more contagious variants – which the vaccines were not designed for – are circulating, and because preventive measures – and adherence to them – varies widely.

WHO has asked for a moratorium on widespread use of booster doses (although it recommends them for immunocompromised people) until the end of 2021; its Director General, Tedros Adhanom Ghebreyesus, said that it is “...unjust and also unfair because we will not stop the pandemic by ignoring a whole continent, and the continent that doesn’t have any manufacturing capacity of other means.”

As of 11 October 2021, after a four-day meeting of its Strategic Advisory Group of Experts, the World Health Organization (WHO) recommends booster doses for:

- Moderately and severely immunocompromised persons, who should be offered an additional dose of all WHO approved vaccines (Johnson and Johnson, Moderna, AstraZeneca/Oxford/Serum Institute of India, Pfizer/BioNTech, Sinopharm and Sinovac), since they are “...less likely to respond adequately to vaccination after the standard primary vaccine series and are at high risk of severe COVID-19 disease.”
- People aged 60 and older who received the Sinovac and Sinopharm vaccines should also get a third dose, though use of other vaccines may also be considered depending on supply and access.⁴⁷

On 9 December 2021, WHO changed its recommendation for the Johnson and Johnson vaccine to include the potential for a second dose: “As vaccine supplies or accessibility improve, countries should consider offering a second dose...[with] an inter-dose interval of 2 to 6 months”⁴⁸

The EMA and the US CDC have issued recommendations for booster dosing. The EMA’s Human Medicines Committee recommends that an extra dose of the Moderna or Pfizer/BioNTech vaccine may be given to people with severely weakened immune systems at least 28 days after their second dose, noting that it is “...important to distinguish between the extra dose for people with weakened immune systems and booster doses for people with normal immune systems.”⁴⁹

After initially limiting people who should get a booster of the Moderna and Pfizer/BioNTech vaccines, the CDC changed its recommendation in November 2021 to include everyone over age 18, six months after their initial vaccination. CDC also recommends a booster for people who received the Johnson & Johnson vaccine at least 2 months after receiving their primary vaccine dose.⁵⁰

Remaining and Evolving Research Questions

Mixing Doses

Mixing different vaccines, called heterologous prime-boost vaccination, is a strategy that has been used to increase immune responses to HIV vaccines. Some countries have mixed different vaccines because of concerns about adverse events in certain groups, supply challenges, or because they believe certain vaccines are more – or less – effective than others. Evidence from several studies supports the safety of dose-mixing (although most research has been limited to mixing the AstraZeneca/Oxford vaccine with an mRNA vaccine).

After concerns about TTS led Sweden to suspend use of the AstraZeneca/Oxford vaccine, more than 100,000 people who got the vaccine were given an mRNA vaccine for their second dose. Researchers in Sweden looked at national health system data to compare outcomes among people who got two doses of the AstraZeneca/Oxford vaccine versus people who got mixed doses. They found that mixed-dose vaccination was significantly more effective for preventing symptomatic COVID-19 than two doses of the same vaccine (68% versus 50%).⁵¹

A French study following 13,121 healthcare workers looked at immune responses among people who got two doses of the Pfizer/BioNTech vaccine or one dose of the Oxford/Astra Zeneca vaccine and one dose of the Pfizer/BioNTech vaccine. Those who had two doses of the same vaccine were twice as likely to become infected with SARS-CoV-2 than those who received mixed doses. Researchers looked at blood samples taken before vaccination, after the first dose, and a month after the second dose, to investigate an immunological basis for the difference in infection rates. Notably, people who got mixed doses had higher titers of neutralizing antibodies (including against the Alpha, Beta, Delta and Gamma variants) and more activated memory B cells than people who got two doses of the same vaccine. The authors suggest that the enhanced protection from vaccine mixing might be attributed to complementarity between the stronger T cell responses induced by the AstraZeneca/Oxford vaccine and the high levels of antibodies induced by mRNA vaccines.⁵²

People Living with HIV

COVID-19 vaccines are safe and recommended for people living with HIV (PLHIV). More data are needed on their efficacy, particularly among people who are not on antiretroviral therapy and PLHIV with a low CD4 cell count and/or a high viral load (although COVID-19 vaccines should also be available to people in these circumstances).

PLHIV are not more likely to become infected with SARS-CoV-2, but they are more likely to fall seriously ill, become hospitalized and are at 30 percent greater risk of death from COVID-19 than people who are HIV-negative.⁵³ WHO recommends that PLHIV should be:

- Prioritized for COVID-19 vaccines;
- Tested and if needed, provided with treatment and management of hypertension and diabetes – since these conditions also increase the risk for severe COVID-19, hospitalization, and death.⁵⁴

The US CDC recommends evaluating the immune status of PLHIV when they are vaccinated.

People with a CD4 cell count of <200 cells/mm³ and/or untreated HIV should receive a third dose of an mRNA vaccine or a second dose of the Johnson & Johnson vaccine.

Boosters, at six months after the second dose, are recommended for PLHIV age 50 and over (and may benefit younger PLHIV with other risk factors for severe COVID-19, including medical conditions or occupations).⁵⁵

People Who Have Recovered From COVID-19

Vaccination is recommended for people who have recovered from COVID-19, although small studies (of less than 500 people) have reported immune responses that persist for six months.^{56,57,58} The duration and robustness of these responses vary quite a bit between people, and may depend on the severity of their illness. A study in the US, published by CDC, estimated that unvaccinated people who were previously infected with SARS-Cov-2 are five times more likely to be hospitalized with COVID-19 than vaccinated people.⁵⁹

The combination of natural immunity and vaccine-induced immunity is likely to be the most effective. An Israeli study found fewer infections with the Delta variant among people who recovered from COVID-19 versus those who received both doses of the Pfizer/BioNTech vaccine - but COVID-19 testing was voluntary, so many asymptomatic or mild infections among previously infected people could have been missed because they may have assumed that they were immune. Notably, the highest protection rate was found among people who had recovered from COVID-19 and received one dose of the Pfizer/BioNTech vaccine.⁶⁰ Another study looking at the impact of previous infection and/or vaccination reported that people who had both natural and vaccine-induced immunity had higher levels of neutralizing antibodies than uninfected, vaccinated people.⁶¹

Vaccine Efficacy Against Long COVID

Long COVID – symptoms that persist for months – affects millions of people worldwide, with researchers estimating that one of every ten people with COVID-19 will develop long-lasting symptoms.⁶² COVID-19 vaccines can prevent Long COVID by lowering the risk of becoming infected with SARS-CoV-2, and they may lower the risk of developing Long COVID. A study of 1,240,009 people in the UK who were using the COVID Symptom Study app found that being fully vaccinated reduced odds of symptoms lasting over 28 days by half.⁶³ A survey of 900 people with lived experience of Long COVID (more than 70% of them for more than nine months) looked at the impact of the vaccine on 14 common symptoms. Results were grouped by the vaccine type (Johnson and Johnson and AstraZeneca/Oxford; mRNA vaccines were considered individually). Most survey participants (770/900) had a single vaccine dose within 60 days of their participation. Overall, 56.7% reported an improvement in symptoms, 24.6% reported no change in symptoms and 18.7% worsened after vaccination. The most improvement was seen after the Moderna vaccine (average of 31% over baseline, and beneficial across all symptoms), followed by the Pfizer/BioNTech vaccine (average of 24.4%) and the viral vector vaccines (average of 22.6%).^{64,65}

Conclusion and ITPC resources

“Vaccines don’t save lives, vaccination does.”⁶⁶

The global pandemic won’t end until there is equitable access to COVID-19 vaccines for everyone, everywhere in the world. Although efforts have been underway to provide vaccines for people in low- and middle-income countries, as of November 2021, only 24% in lower-middle income countries and 3% of people in low-income countries have received them.⁶⁷ While some high-income countries grapple with vaccine hesitation and the anti-vax movement, people in low- and middle-income countries are falling ill and dying without access to vaccines. Getting vaccines where they are needed involves holistic and practical short-, medium- and long-term strategies.

These strategies include overcoming intellectual property barriers that keep vaccines unaffordable; facilitating local production (which has economic benefits and could remedy supply shortages); preparing healthcare systems and their staff to expand off-site delivery, and getting people ready to receive them. People need access to clear, accurate and community-friendly information, delivered respectfully from trusted sources – otherwise, misinformation will flourish and vaccine uptake will be suboptimal.

ITPC RESOURCES

Information about COVID-19 is changing frequently. The International Treatment Preparedness Coalition provides current updates on research, policy, treatment, and vaccines on our website at: [ITPCglobal.org/covid-19/](https://www.itpcglobal.org/covid-19/)

For more information on how to fight for access to COVID-19 vaccines and other life-saving medicines, see [MakeMedicinesAffordable.org](https://www.makemedicinesaffordable.org/)

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