COVID-19 Vaccines—All You Want to Know

Akira A. Shishido, MD[1,2] Ashley H. Barnes, MD[1] Shivakumar Narayanan, MD[1] Joel V. Chua, MD[1]

[1] Division of Clinical Care and Research, Institute of Human Virology, University of Maryland School of Medicine, Baltimore, Maryland
[2] Division of Infectious Diseases, Virginia Commonwealth University, Richmond, Virginia

Address for correspondence Joel V. Chua, MD, Division of Clinical Care and Research, Institute of Human Virology, University of Maryland School of Medicine, Baltimore, MD 21201 (e-mail: jchua@ihv.umaryland.edu).

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Abstract

The severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) pandemic has led to an unprecedented public health crisis. The collective global response has led to production of multiple safe and effective vaccines utilizing novel platforms to combat the virus that have propelled the field of vaccinology forward. Significant challenges to universal vaccine effectiveness remain, including immune evasion by SARS-CoV-2 variants, waning of immune response, inadequate knowledge of correlates of protection, and dosing in special populations. This review serves as a detailed evaluation of the development of the current SARS-CoV-2 vaccines, their effectiveness, and challenges to their deployment as a preventive tool.

Keywords
- COVID-19
- SARS-CoV-2
- vaccines
- variants
- immunity

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) was first reported in Wuhan, China at the end of 2019.[1] SARS-CoV-2 is a single-stranded RNA betacoronavirus that has swept the globe creating an unprecedented public health crisis. As of June 1, 2022, two and a half years after the initial reports, there have been over 500 million cases with close to 6.3 million deaths worldwide.[2] The pandemic has spurred a massive global effort to develop effective countermeasures to limit the spread of the disease and associated mortality. This has led to testing and approval of multiple effective vaccines at an unprecedented rate. This review serves as a detailed evaluation of the development and clinical efficacy of the COVID-19 vaccines and the challenges ahead.

Vaccine Development

The global COVID-19 pandemic forced a paradigmatic change in the vaccine development and deployment process. Traditionally, phased studies proceed sequentially to generate efficacy data followed by large-scale production.[3] While rooted in safety, this process takes years to produce a single viable product.[3] SARS-CoV-2 shifted development to a "Pandemic Paradigm" in which preclinical development, phased trials, and large-scale manufacturing all advance simultaneously in an expedited timeline. This is a challenging endeavor needing a coordinated effort and entails high risk to developers.[3]

Formal efforts for a SARS-CoV-2 vaccine began in January 2020.[4] Within 2 months, 20 additional candidate vaccines began preclinical studies.[4] The first phase I clinical trials began in March 2020, less than 10 weeks after the first SARS-CoV-2 genetic sequences were released, spurring the most expeditious deployment of clinical trials in history.[3]

The CARES Act (Coronavirus Aid, Relief, and Economic Security Act) passed on March 27, 2020, provided $18 billion in funding for vaccine development.[5] Operation Warp Speed was a public–private partnership initiated by the United States on May 15, 2020 to accelerate the development, manufacturing, and distribution of COVID-19 vaccines within the United States.[5] The program directly funded several of the largest vaccine developers including Janssen Pharmaceutical, AstraZeneca, Moderna, and Novavax, and ultimately led to the development and distribution of effective vaccines.[5,6]

The Coalition for Epidemic Preparedness Innovation (CEPI), an international nongovernmental organization with multinational funding, led the global effort to coordinate the development of successful COVID-19 vaccines.[3] More recently, the U.S. government pledged $4 billion to COVAX, an international partnership led by CEPI and the World Health Organization (WHO) charged with ensuring global vaccine security.[7]

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Rapid generation of preclinical data led to phase 1 trials for COVID-19 vaccines beginning in March 2020. Stacked phase 2 and phase 3 clinical trials ran concurrently leading to the publication of several peer-reviewed trial results at the end of 2020. On November 9, 2020, Pfizer and BioNTech announced results from the phase 3 study of the BNT162b2 vaccine trial reporting >90% protection against COVID-19.[8] On December 2, 2020, UK regulators granted emergency-use authorization to BNT162b2, only 7 months after the onset of clinical trials and less than a year since the release of the SARS-CoV-2 genetic sequence.[9–11] As of June 2022, a total of 359 vaccine candidates have been developed, 161 remained in clinical development, and 32 have been authorized or approved for use in at least one country (►**Table 1**).[4,12,13]

COVID-19 Vaccine Platforms

SARS-CoV-2 possesses four structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins (►**Fig. 1**).[14,15] The canonical S protein binds angiotensin-converting enzyme 2 (ACE2) in human respiratory cells and facilitates membrane fusion and cell entry.[16] Studies on the original SARS-CoV found that vaccines encoding the S protein elicited potent immune responses.[17–19] SARS-CoV-2 vaccine candidates generally target either the entire S protein or the receptor-binding domain (RBD) of the S protein.[14]

Global efforts by developers have led to development of a diverse array of SARS-CoV-2 vaccine platforms and candidates. These included candidates from the well-established platforms of inactivated vaccines and subunit vaccines but also the novel nonreplicating viral vector vaccines and nucleic acid vaccines (►**Fig. 2**).

Inactivated vaccines deploy a killed pathogen to deliver multiple antigens into the host to produce an immune response.[14] The BBIBP-CorV, CoronaVac, and Covaxin vaccines are currently authorized inactivated SARS-CoV-2 vaccines. The general concerns of such vaccines are that multiple antigens may dilute the immune response to the primary antigen and that they require biocontainment to grow active pathogens safely.

Subunit vaccines deliver isolated viral proteins into the host allowing for a targeted immunologic response. While generally considered a safer platform than other vaccines given their limited antigenic profile, subunit vaccines can be complex, and expensive to produce.[14] The Novavax COVID-19 vaccine, NVX-CoV2373, is a subunit vaccine that takes a novel approach and further assembles genetically modified S proteins harvested from moth cells into virus-like nanoparticles.[20]

AZD1222, Ad26.COV2.S, and Sputnik V are nonreplicating adenoviral-vectored vaccines currently in active use. Viral vector vaccines can deliver antigens and genetic code directly into cells. Human cells then express viral proteins prompting an immunologic response.[14] Prior to the COVID-19 pandemic, the only adenovirus vector vaccine approved for use in humans was the Ebola vaccine Ad26.ZEBOV.[21,22] This novel platform mitigates the risk of viral pathogenicity by eliminating the adenoviral gene E1 required for viral replication.[23] Additionally, the Sputnik V and Gam-COVID-Vac vaccines employ two varying adenovirus serotypes, which are intended to overcome any adenovirus-directed immunity that may negate an effective immune response.[24,25]

The nucleic acid vaccines deliver viral genetic material directly into human cells under the protection of a lipid nanoparticle prompting cellular viral protein expression and immunologic response.[14,26] To date, the only approved or authorized nucleic acid vaccines are the Pfizer/BioNTech BNT162b2 and Moderna's mRNA-1273.[13,27–29] The mRNA vaccines have revolutionized the field of vaccinology given the mounting evidence of the platform's high potency, the ability for rapid development, and cost-efficient production.[14] While previously studied for utilization in oncology and against other infections, mRNA vaccines had not previously been approved or authorized prior to COVID-19.[26]

Vaccine Synopsis and Efficacy

Given the significant number of successful vaccines in active use, this review will focus on the 10 most widely distributed vaccines by country count as of June 2022. ►**Table 2** summarizes published efficacy data and basic details for these vaccines. Estimated efficacy in the initial clinical studies of these vaccines may be modified in later phases of the pandemic due to changes in predominant circulating variant, rising background immunity due to prior infection, or vaccination. Evolving data have to be compared and contrasted accounting for these factors, as well as balancing study design, ascertainment of efficacy end points, and clinical relevance of these endpoints (i.e., protection against severe infection and mortality vs. prevention of infection) We address adverse effects (AEs), duration of immunity, activity against variants of concern (VOCs), and special populations in subsequent sections.

Taken together, comparative studies have found the mRNA-based COVID-19 vaccines demonstrated the highest overall efficacy (>90%) after two doses against symptomatic COVID-19 infection during the initial waves of the pandemic, followed by nonreplicating adenoviral vector vaccines and inactivated vaccines.[30,31] A pooled subgroup analysis of multiple trials suggests the vaccines provide approximately 84% protection against all SARS-CoV-2 infection, 89% protection against symptomatic cases, and 66% protection against asymptomatic cases overall.[31] All vaccines display high efficacy against severe disease with none appearing to have a statistically significant advantage over another when directly compared.[32] AZD1222, the Sputnik, and Covaxin vaccines are among the least expensive, while BBIBP-CorV and mRNA-1273 are among the most expensive (►**Table 2**).[33] The mRNA-based vaccines possess the most advanced cold chain requirements (−70°C for BNT162b2 for long-term storage), while CoronaVac can reportedly be stored at room temperature for up to 42 days.[33–35] Real-world vaccine effectiveness is affected by many variables including VOCs, duration of protection, underlying immunity, and comorbidities (►**Fig. 3**). Further discussion regarding these variables is in subsequent sections.

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Table 1 Current approved and authorized COVID-19 vaccines as of January 25, 2022 (compiled and modified from multiple sources)[4,13,27,28]

Name	Primary developers	Country of origin	Countries authorized/ approved
COVID-19 Vaccine AstraZeneca (AZD1222); also known as Vaxzevria and Covishield[217]	BARDA, OWS	The United Kingdom	137
Comirnaty (BNT162b2)[66]	Pfizer, BioNTech; Fosun Pharma	Multinational	136
COVID-19 Vaccine Janssen (JNJ-78436735; Ad26.COV2.S)[218–220]	Janssen Vaccines (Johnson & Johnson)	The Netherlands, the United States	106
BBIBP-CorV/NVSI-06–07[221,222]	Sinopharm	China	88
Moderna COVID-19 Vaccine (mRNA-1273); also called Spikevax[64,65]	Moderna, BARDA, NIAID	The United States	85
Sputnik V[25,223,224]	Gamaleya Research Institute, Acellena Contract Drug Research and Development	Russia	74
CoronaVac[225,226]	Sinovac	China	52
NVX-CoV2373 (Nuvaxovid; Covovax in India)[227]	Novavax; CEPI, Serum Institute of India	The United States	32
Sputnik Light[228,229]	Gamaleya Research Institute, Acellena Contract Drug Research and Development	Russia	24
Covaxin (BBV152)[67]	Bharat Biotech, ICMR; Ocugen; ViroVax	India	13
Convidicea (PakVac, Ad5-nCoV)[230,231]	CanSino Biologics	China	10
Abdala (CIGB 66)[232]	Center for Genetic Engineering and Biotechnology	Cuba	7
EpiVacCorona (NCT04780035; NCT05021016)[233]	FBRI	Russia	4
Soberana 02/Soberana Plus (no published studies)[234,235]	Finlay Institute of Vaccines; Pasteur Institute	Cuba, Iran	4
CoviVac[236]	Chumakov Federal Scientific Center for Research and Development of Immune and Biological Products	Russia	3
ZF2001 (ZIFIVAX)[237,238]	Anhui Zhifei Longcom Biopharmaceutical, Institute of Microbiology of the Chinese Academy of Sciences	China, Uzbekistan	3
WIBP-CorV[222]	Sinopharm (Wuhan)	China	2
QazVac (QazCovid-in)[239,240]	Research Institute for Biological Safety Problems	Kazakhstan	2
KCONVAC[241,242]	Minhai Biotechnology Co.; Kangtai Biological Products Co. Ltd.	China	2
MVC-COV1901[243,244]	Medigen Vaccine Biologics Corp.; Dynavax	Taiwan	2
VLA2001	Valneva, UK National Institute for Health Research, Dynavax	France, the United States	2
Aurora-CoV[245,246]	FBRI	Russia	1
COVIran Barekat[247,248]	Shifa Pharmed Industrial Group	Iran	1

(*Continued*)

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Table 1 (*Continued*)

Name	Primary developers	Country of origin	Countries authorized/ approved
IMBCAMS[249–251]	Chinese Academy of Medical Sciences, Institute of Medical Biology	China	1
ZyCoV-D[252]	Zydus Cadila	India	1
Spikogen (COVAX-19)[253]	Vaxine Pty Ltd.; CinnaGen	Iran	1
Turkovac (ERUCOV-VAC)[254,255]	Health Institutes of Turkey	Turkey	1
Corbevax[256]	Biological E, Baylor College of Medicine, Dynavax, CEPI	India, the United States	1
Recombinant COVID-19 Vaccine (CHO cell)[257,258]	National Vaccine and Serum Institute	China	1
Razi CoV Pars[259,260]	Razi Vaccine and Serum Research Institute	Iran	1
Covifenz	Medicago, GSK, Dynavax	Canada	1
Noora	Baqiyatallah University of Medical Sciences	Iran	1

Abbreviations: FBRI, Federal Budgetary Research Institution State Research Center of Virology and Biotechnology; GSK, Glaxo-Smith-Kline.

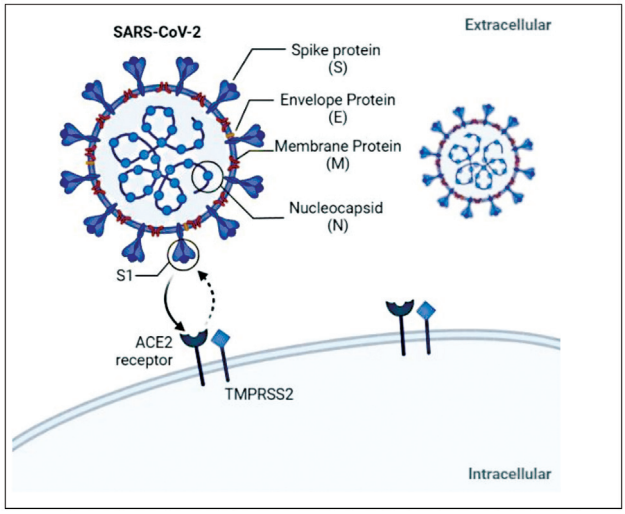

Fig. 1 Structure of SARS-CoV-2 and human ACE2 receptor. Illustration created by authors using BioRender.com. ACE2, angiotensin-converting enzyme 2; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2.

Immunogenicity

All COVID-19 vaccines in active use provide robust antibody responses at varying levels. Antispike immunoglobulin G (IgG) correlates with neutralizing antibody levels and generally are similar to or higher than those induced by infection.[36] A recent comparative analysis among COVID-19 vaccine candidates found that the Moderna mRNA-1273 achieved the highest measurable neutralizing antibody titer, followed in order by the Pfizer/BioNTech BNT162b2, Sputnik V, Bharat Biotech BBV152, Janssen Ad26, and AstraZeneca AZD1222.[37] In multiple-vaccine-dosed subjects, neutralizing antibody titers were highest in the Novavax NVX-CoV2373 and Moderna mRNA-1273-boosted groups, followed by Ad26, AZD1222, and BNT162b1. Multiple studies have shown that neutralizing antibody titers appear to decrease with age, with measured decreases at >55 years old and >70 years old.[38–45] Sex, prior infection, and immunosuppression are additional host factors which may affect immune response.[46]

Vector-directed immunity may have affected the AZD1222 vaccine response through pre-existing neutralizing antibodies to the vector.[47] Additionally, longer spacing between doses (84 vs. 42 days) resulted in twofold higher S protein IgG titers.[47,48] This could be attributable to antivector immunity blunting immune response to subsequent dose in the early dose group, but then waning and allowing for a more robust response in the delayed group.[49] These effects were not observed in the Sputnik V studies, possibly due to variation of the adenoviral vector within the series.[25] While only interim results are currently available, Janssen reports similar S protein antibody levels among trial participants regardless of pre-existing Ad26 antibodies.[50]

T-Cell Response and Correlates of Protection

T-cell response appears to be an increasingly important component of immune protection from COVID-19.[51] T-cell responses can be detected in asymptomatic individuals exposed to family members with COVID-19, among whom only 60% may have detectable SARS-CoV-2 antibodies.[52,53] These data suggest that T-cell response may be more important than humoral immunity in the clearance of infection. All COVID-19 vaccines in active use elicit a robust T-cell response.[54] Generally, the vaccines induce a T helper type 1 (T_H1)-skewed T-cell immune response with S protein-specific $CD8^+$ and $CD4^+$ T-cell expansions.[37,54,55] A majority of BNT162b2 vaccine

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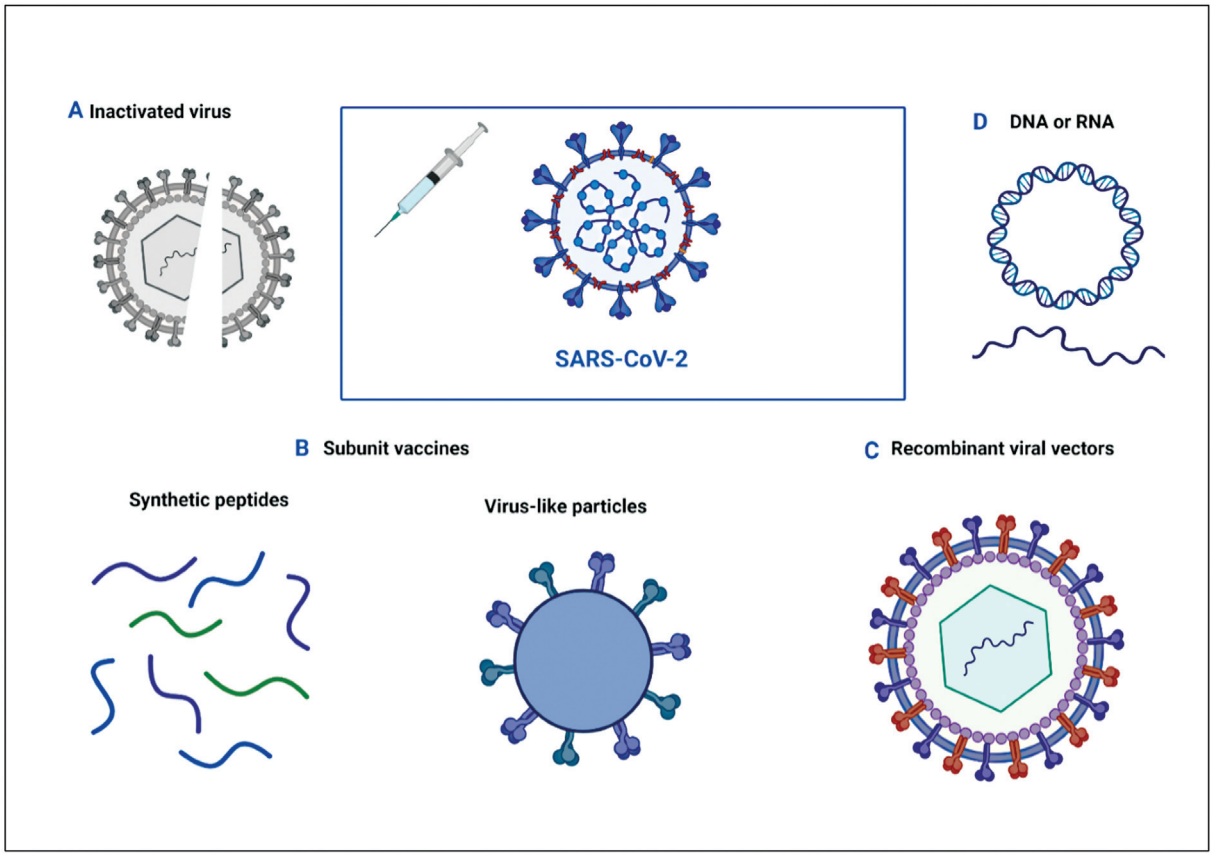

Fig. 2 COVID-19 vaccine platforms. Illustration created by authors using Biorender.com (modified from Dong et al[14]). COVID-19, novel coronavirus disease 2019.

recipients develop S protein antibodies after 10 days, but 100% of vaccinees developed S protein-specific T-cells by the same day.[56] While mRNA vaccines elicit the highest measurable antibody titers, the AZD1222 adenoviral-vectored vaccine elicited higher T-cell responses.[37,57,58]

No widely acknowledged correlate of durable protection against COVID-19 currently exists. Two studies have successfully found correlations between neutralizing antibody titers and protection from infection and severe disease for ancestral and α strains.[36,59] However, these studies also found waning antibody levels over time and decreases in efficacy against VOCs. Given the established evolutionary nature of the pandemic with newly emerging VOCs that possess mutant S proteins, measurable antibody titer may not be a sustainable or reliable correlate of protection.

However, since COVID-19 vaccines appear to retain protection against severe disease from VOCs that evade humoral immunity, it is speculated that cellular responses may account for this sustained protection.[54] This concept is supported by the finding that while vaccine-generated antibodies have reduced neutralizing capacity against VOCs, there appears to be no reduction in CD4+ T-cell activation in response to variant antigens.[60] Moreover, a study examining CD8+ T-cell activity in convalescent patients found responses to virtually all tested mutations in the S protein, suggesting retained cell-mediated immunity (CMI) against new variants.[61] Therefore, CMI may provide a more reliable correlate of protection to COVID-19 than antibody response in the wake of actively evolving S proteins.

Adverse Effects

As of June 2022, 65.7% of the world population has received at least one dose of a COVID-19 vaccine; 11.8 billion doses have been administered globally with 5.7 million doses being administered each day.[62] Between the initial safety and efficacy trials and the real-world data that followed, it is clear that COVID-19 vaccines have a favorable safety profile. While all the vaccines are associated with mild local and systemic reactions, serious side effects are rare (<5/million). To varying degrees, all the vaccines are associated with mild injection-site reactions (e.g., pain, erythema), as well as systemic reactions most commonly fatigue, headache, fevers, and chills (►**Table 3**). Younger age, female sex, prior COVID-19, and type of vaccine and dose are associated with an increased risk of AEs.[63] In general, the mRNA vaccines appear to have the highest rate of mild AE with 70 and 78% of vaccinees reporting pain at the injection site for BNT162b2 and mRNA-1273 respectively, and 55 and 72% reporting fatigue.[64–66] The inactivated vaccine BBV152 reportedly has the lowest overall rate of mild AE.[67] The primary safety issues identified to date include anaphylaxis (5/million),[68] myocarditis associated with the mRNA vaccines (50–105/million based on the U.S. National Vaccine Adverse Event Reporting System [VAERS] data in select age

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Table 2 Summary of the 10 most widely distributed COVID-19 vaccines

Name	Platform	Dose	Trial size	Age (y)	Efficacy	Variants during trial	Benefits	Drawbacks
COVID-19 vaccine AstraZeneca (AZD1222); also known as Vaxzevria and Covishield[48,217]	Nonreplicating adenovirus vector (AZD1222)	Two doses 4 to 12 weeks apart	32,451; 17,178	≥18	67–74%[48] protection from symptomatic COVID-19 and positive PCR result.[48,217] 100% protection from hospitalization or severe disease	ALPHA (B.1.1.7), BETA (B.1.351), GAMMA (P.1), B.1.427/B.1.429, P.2, B.1.526, and C.37	Requires standard refrigeration to 2–8°C for transport and storage.[33] $5/course[33]	Pre-existing and vector-directed immunity may reduce response.[261] Complex manufacturing process.[261] VITT/CVST 0.73–11 per 100k vaccinations[74,78,262]
Comirnaty (BNT162b2)[66]	mRNA	2 doses 21 days apart	43,548	>16	95% protection from symptomatic COVID-19 and positive PCR result.[66] >95% protection from hospitalization or severe disease	BETA (B.1.351), GAMMA (P.1), B.1.427/B.1.419, P.2, and B.1.526	Highly effective and serious adverse effects are rare. $14/course[33]	Requires refrigeration to − 70°C for transport and storage. Can be stored in dry ice for up to 30 days. Can be stored at 2–8°C for 5 days[33,34]
COVID-19 Vaccine Janssen (JNJ-78436735; Ad26.COV2.S)[218–220]	Nonreplicating adenovirus vector (Ad26)	1 dose	44,325	≥18	66%[218–220] protection from symptomatic COVID-19 and positive PCR result. 85% protection from hospitalization or severe disease	BETA (B.1.351), GAMMA (P.1), B.1.427/B.1.429, P.2, B.1.526, and C.37	Requires standard refrigeration to 2–8°C for transport and storage.[33] $9/course[33]	Pre-existing immunity may reduce response.[261] Complex manufacturing process.[261] VITT/CVST 0.73–11 per 100k vaccinations[74,78,262]
BBIBP-CorV/NVSI-06–07[221,222]	Inactivated vaccine	2 doses 21 days apart	40,411	≥18	78%[222] protection from symptomatic COVID-19. 100% protection from hospitalization or severe disease	Not reported	Requires standard refrigeration to 2–8°C for transport and storage[33]	Theoretical risk of vaccine-enhanced disease.[261] $62/course[33]
Moderna COVID-19 Vaccine (mRNA-1273); also called Spikevax[64,65]	mRNA	2 doses 28 days apart	30,420	≥18	94%[64,65] protection from symptomatic COVID-19 and positive PCR result. 100% protection from hospitalization or severe disease	B.1.427, B.1.429, and B.1.526	Highly effective and serious adverse effects are rare	Requires refrigeration to −20°C for transport and storage. Can then be stored at 2–8°C for 30 days.[33,34] $31/course[33]
Sputnik V[25,223,224]	Nonreplicating adenovirus vector (rAd26 and rAd5)	2 doses 21 days apart	21,977	≥18	92% protection from symptomatic COVID-19 and positive PCR result. 100% protection from hospitalization or severe disease Note: 2 patients in vaccine arm died from COVID-19 early in course	Not presented in the interim analysis.	Requires standard refrigeration to 2–8°C for transport and storage.[33] $6/course[33]	Only interim analysis published to date. Pre-existing immunity may reduce response[261]
CoronaVac[225,226]	Inactivated vaccine (formalin with alum adjuvant)	2 doses 14 days apart	>10 million	≥16	65% (Chile)[17]; 84%[18] (Turkey) protection from symptomatic COVID-19 88% (Chile); 100% (Turkey) against severe disease	GAMMA (P.1) and P.2	Lasts up to 3 years at 2–8°C. Can be stored at room temperature up to 42 days[35]	$21/course[33]
NVX-CoV2373 (Nuvaxovid; Covovax in India)[227]	Recombinant nanoparticle vaccine	2 doses 21 days apart	15,187	≥18	89%[227] protection from symptomatic COVID-19 and positive PCR result.	ALPHA (B.1.1.7), BETA (B.1.351), B.1.427/B.1.429, and B.1.526	Requires standard refrigeration to 2–8°C for	Complex manufacturing and adjuvants may be required[261]

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Table 2 (*Continued*)

Name	Platform	Dose	Trial size	Age (y)	Efficacy	Variants during trial	Benefits	Drawbacks
					100% protection from hospitalization or severe disease Note: 1 patient in vaccine arm died from COVID-19 early in course		transport and storage.[33] $6/course[33]	
Sputnik Light[228,229,263]	Nonreplicating adenovirus vector (rAd26 component of Sputnik V)	1 dose	6,000	≥18	Only phase 1/2 trial published.[228] Phase 3 trial ongoing[263]	N/A	$6/course[33]	Requires refrigeration to −18°C for transport and storage[33] No published phase 3 clinical trials examining the singular component
Covaxin (BBV152)[67]	Inactivated vaccine	2 doses 28 days apart	24,419	≥18	78%[67] protection from symptomatic COVID-19 and positive PCR result. 100% protection from hospitalization or severe disease	B.1.1.7, DELTA (B.1.617.2), and B.1.617.1	Requires standard refrigeration to 2–8°C for transport and storage.[33] $6/course[33]	Theoretical risk of vaccine-enhanced disease[261]

Abbreviations: CVST, central venous sinus thrombosis; VITT, vaccine-induced thrombotic thrombocytopenia.

cohorts),[69–72] vaccine-induced immune thrombotic thrombocytopenia (VITT; 4/million) with the adenoviral vectored vaccines,[73–80] and rare cases of inflammatory demyelinating syndromes.[81–89]

Anaphylaxis

Shortly after the authorization of the mRNA vaccines, cases of anaphylaxis were reported.[90,91] Analysis conducted with VAERS found rates of 4.7 cases/million Pfizer-BioNTech vaccine doses and 2.5 cases/million Moderna vaccine doses administered.[92] The majority of reactions occurred in women (>94%), most of whom reported a history of allergies or allergic reactions.[92] Symptoms occurred within a median of 10 minutes after vaccination and responded to standard management with epinephrine and antihistamines.[92] It is not clear that a singular component of the vaccines is responsible for the reactions, though polyethylene glycol (PEG) has been implicated.[93,94] Patients with a history of PEG allergy should not receive an mRNA vaccine.[95] Overall, the incidence of severe allergic reactions is low, and no deaths have been reported.[68,92]

Myocarditis

Early reports of vaccine-associated myocarditis surfaced in April 2021 and were temporally linked to mRNA vaccination.[69,96] Subsequently, over 1,500 cases of myocarditis have been reported through the VAERS database.[71,97] Cases predominantly occur in young men (median age: 21 years, 76% males).[97] The majority of cases (88%) occur within a few days of the second dose of mRNA vaccination (median: 2 days).[71,97] While a higher number of cases of myocarditis have been reported with BNT162b2 compared with mRNA-1273 (77 vs. 23%), overall rates appear similar given the greater number of BNT162b2 doses administered in the United States compared with mRNA-1273.[71,97,98] Rates of myocarditis decrease with age ranging from 52 cases per million in 16- to 17-year-olds to 0.18 cases per million doses in patients greater than 65.[71] Patients are admitted to the hospital for a median of 3 days with chest pain, elevated troponins, and EKG (electrocardiogram) changes.[97] Diagnosis can be confirmed with magnetic resonance imaging showing late gadolinium enhancement.[71,97] There is no standard for management, though colchicine, aspirin, intravenous immunoglobulin have been reported.[97] Overall prognosis is excellent, with 87% having resolution of symptoms by hospital discharge, though deaths have been reported in extremely rare cases.[71,99,100]

VITT/CVST

In early March 2021, the European Medicines Agency (EMA) announced findings of a rare thrombosis with thrombocytopenia syndrome in patients who had received the AZD1222 vaccine.[79,101] The syndrome, now referred to as VITT, has been associated with both the Ad26.COV2.S and AZD1222 adenoviral-vectored vaccines at an estimated rate of 1 per 100,000 to 200,000 vaccine exposures.[80,102,103] Typical onset occurs roughly 8 and 10 days after Ad26.COV2.S and AZD1222 vaccinations, respectively. Most patients do not

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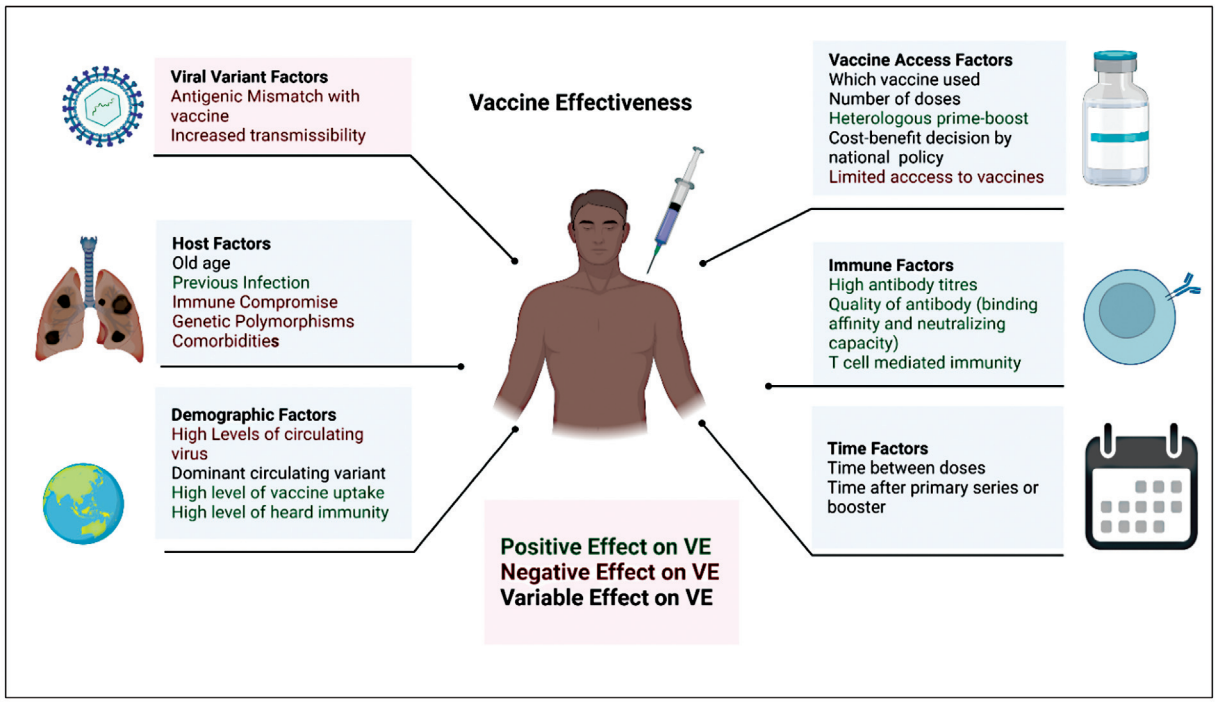

Fig. 3 Factors influencing vaccine effectiveness. Illustration created by authors with Biorender.com (modified and updated with new data from Tregoning et al[216]).

have a history of coagulation disorders.[103] The most severe cases present with cerebral venous sinus thrombosis (CVST), though other thrombotic events including venous thromboembolism, abdominal vein clots, and arterial clots have been reported.[75,76,104] The primary risk factors for VITT appear to be female sex (ratio 2.5:1) and age younger than 60 years.[103] A systematic review of COVID-19 VITT literature to date found that among 36 patients with CVST, 16 developed intracranial hemorrhage and/or subarachnoid hemorrhage.[80] Among 54 patients included in the study 21 (38.8%) died.[80] Out of concern for VITT, the Food and Drug Administration has limited Ad26.COV2.S only to persons who are unable or unwilling to get an mRNA vaccine in the United States.

VITT appears to clinically resemble heparin-induced thrombocytopenia.[78,80,103] VITT patients generate autoantibodies against PF4 but do so in the absence of heparin exposure possibly due to an unidentified antigen in the adenoviral vaccines or expressed by infected cells by the vaccine.[80,103,104] PF4–IgG crosslinks with FcGTIIa on platelets causing activation and thrombosis.[103–106]

Neurologic Syndromes

Cases of Guillain–Barre syndrome have been reported in association with AZD1222, BNT162b2, and Ad26.COV2.S vaccination.[81–83,107,108] In limited data, there appears to be no predilection for age or gender, and cases occur after the first dose of vaccine at a rate of approximately 0.006%.[81,107] A recent analysis of the United Kingdom's National Health Service database found that the first dose of AZD1222 is associated with a risk of approximately 5.8 cases per million doses, while the first dose of BNT162b2 showed no excess risk.[109] Similarly, acute transverse myelitis has been reported in association with the AZD1222, Ad26.COV2.S, mRNA-12273, and CoronaVac vaccines.[84–89] Time of onset varies from 3 hours to 39 days.[81] Outcome data are incomplete, but generally cases appear severe with limited neurologic recovery.[81,107] There have additionally been case reports of encephalitis associated with AZD1222[110] and facial nerve palsies with BNT162b2.[111] While not formally established, the presumed mechanism is induction or exacerbation of autoimmunity via antigenic stimulation with vaccination.

Lymphadenopathy

BNT162b2, mRNA-1273, and AstraZeneca AZD1222 have been associated with reactive lymphadenopathy.[112] Generally, it occurs in the ipsilateral axilla to the side of vaccination 2 to 4 weeks after vaccination.[112] While benign, lymphadenopathy has complicated screening or follow-up cancerous patients—therefore, it is recommended that the vaccine should be injected in the arm contralateral to the primary or suspected malignancy.[112]

Variants of Concern

SARS-CoV-2 variants with S protein mutations that alter binding to both ACE2 and neutralizing antibodies have emerged with the progression of the pandemic. Specifically, VOCs designated by the WHO are variants that have demonstrated increased transmissibility, virulence, or ability to overcome public health countermeasures.[113] Newer variants have been associated with decrease in vaccine efficacy against infection and symptomatic disease (►**Table 4**). Initial

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Table 3 Local, systemic, and notable adverse effects of COVID-19 vaccines

Name	Local	Systemic	Notable
COVID-19 Vaccine AstraZeneca (AZD1222); also known as Vaxzevria and Covishield[48,217]	• Pain at injection site (83%)[264]	• Headache (70%) • Fatigue (68%)[264]	• Thrombocytopenia, thrombosis, and bleeding 0.73–11 per 100k vaccinations.[74,78,262] • Case reports of Guillain–Barre syndrome and transverse myelitis occurrence after vaccination.[82,87] • No associations with infertility, miscarriage, or stillbirth[265]
Comirnaty (BNT162b2)[66]	• Pain at injection site (70%)[66]	• Fatigue (51–59%), headache (39–52%), more common after dose 2 and in >55[66] • Allergy/anaphylaxis 4.7 cases/million vaccinations[68,92]	• Myocarditis 2.13 per 100k persons[69,70,266] • Case reports of facial nerve palsy[111]
COVID-19 Vaccine Janssen (JNJ-78436735; Ad26.COV2.S)[218–220]	• Pain at injection site (49%)[218]	• Headache (39%) • Fatigue (38.2%) • Myalgia (33.2%) • Nausea (14.2%)[218]	• VITT and CVST estimated 1 event per 100,000 vaccine exposures, more common in women and generally occurs 4–30 days after vaccination[80,267–269]
BBIBP-CorV/NVSI-06–07[221,222]	• Pain at injection site (19%).[221,222,270]	• Headache (13%) • Fever (1%)[221,222,270]	• One report of inflammatory demyelination[271]
Moderna COVID-19 Vaccine (mRNA-1273); also called Spikevax[64,65]	• Pain at injection site (78%).	• Fatigue (72%) • Headache (67%) more common after dose 2[65] • Allergy/anaphylaxis 2.5 cases/million vaccinations[68,92]	• Myocarditis 2.13 per 100k persons[69,70,266] • Reports of VITT, estimated 0.00855 per million vaccine doses[269]
Sputnik V[25,223,224]	• Contact dermatitis (3.3% • Injection-site reaction (0.5%)[25]	• Flu-like illness (15.2%) • Headache (2.9%)[25]	• Only interim phase 3 trial results published as of June 2022 • Analysis of Russian social media platform suggested higher levels of mild adverse events including pain (43%), fatigue (54%), and headache (79%)[272]
CoronaVac[225,226]	• Pain at injection site (2.4%)[225]	• Fatigue 8.2% • Myalgia (4%) • Chills (2.5%) • Nausea (1.8%)[225]	• Reported case of deafness[273]
NVX-CoV2373 (Nuvaxovid; Covovax in India)[227]	• Tenderness (76%) • Pain at injection site (21%)—more common after dose 2[227]	• Headache (25%) • Muscle pain (21%) • Fatigue (19%)[227]	• One report of myocarditis[72,227]
Sputnik Light[228,229,263]	• Pain at injection site (6.4%) • Redness (0.9%)[141]	• Flu-like syndrome (49.1%) • Fatigue (5.5%) • Headache (4.5%)[228]	
Covaxin (BBV152)[67,264]	• Injection site pain (3.4%)—more common after dose 1[67]	• Headache <1%[67] • Fever <1%[67] • Fatigue <1%[67] • Myalgia <1%[67]	

Abbreviations: CVST, central venous sinus thrombosis; VITT, vaccine-induced thrombotic thrombocytopenia.

efficacy estimates from clinical trials have not been replicated in subsequent real-world effectiveness studies and epidemiologic data with protection being lower due to immune escape by subsequent variants. However, while protection against infection and symptomatic disease waned, protection from severe disease and death was preserved for all VOCs. As discussed earlier, it is likely that CMI plays a large role in immune protection against severe disease given this protection is preserved despite lower binding affinity and neutralizing ability of vaccine-induced antibodies against

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Table 4 The activity of COVID-19 vaccines against notable variants of concern (VOCs)

Name	Alpha (B.1.1.7)	Beta (B.1.351)	Delta (B.1.617.2)	Omicron (B.1.1.529)
COVID-19 Vaccine AstraZeneca (AZD1222); also known as Vaxzevria and Covishield	A post-hoc analysis of fully vaccinated participants showed reduced efficacy against symptomatic NAAT+ COVID-19: 70.4 vs. 81.5% in non-Alpha, but 100% retained efficacy against severe disease as no participants were hospitalized or died[274]	A randomized control trial of 2,026 fully vaccinated adults in South Africa showed an efficacy of 10.4%. However, it appeared to retain efficacy against severe disease as no participants were hospitalized or died[275]	Case–control studies showed mildly reduced protection from infection (60–70%) but preserved effectiveness against severe COVID-19 in fully vaccinated patients (>90%)[276–278] Meta-analysis suggests 80% efficacy against infection and 91% efficacy against severe illness/death[279]	Significantly reduced efficacy against symptomatic disease with primary (2 dose) series[115,280] A third dose was shown to increase neutralizing antibodies against Omicron in an in vitro preprint study[281]
Comirnaty (BNT162b2)	Prospective cohort showed 85% effectiveness protection from infection—did not assess severe disease[282] An observational study in Israel suggested 97% effectiveness against hospitalization or death[283] An observational study in Qatar showed 90% efficacy against infection and 100% efficacy against severe disease[284] Test-negative case–control study in Ontario suggested 90% protection against infection and 100% infection against severe disease[285]	An observational study in Qatar showed 75% efficacy against infection and 100% efficacy against severe disease[284] A test-negative case–control study in Canada suggested 90% protection against infection and 100% infection against severe disease[285]	A test-negative case–control study showed slightly reduced effectiveness against infection (88%)—did not assess severe disease[277] A case–control study in UK suggested 96% effectiveness against hospitalization[278] A test-negative case–control study in Scotland showed 79% effectiveness against infection[276] A retrospective cohort study suggested 93% effectiveness against infection and hospitalization; protection against infection dropped to 53% at 4 months, but protection against hospitalization remained high (93%) up to 6 months[286] Meta-analysis suggests 84% efficacy against infection and 96% efficacy against severe disease/death[279]	A test-negative case–control study showed vaccine effectiveness against infection ranges from 20 to 80% depending on time after 2-dose series but is restored to 80% with a booster—severe disease not assessed[115]
COVID-19 Vaccine Janssen (JNJ-78436735; Ad26.COV2.S)	Cohort study in the United States showed 74% effectiveness against infection[220]	Phase 3 trial suggested reduced efficacy against infection (61%) but retained protection from severe disease (82%)[218]	71% efficacy against infection and >90% protection against mortality according to a news release[287]	Significant breakthrough infections and hospitalizations, but preliminary data suggest 85% protection against hospitalization with booster[288,289]
BBIBP-CorV/NVSI-06–07	Preclinical studies suggest slightly reduced neutralizing antibody titers[290,291]	Preclinical studies suggest reduced neutralizing antibody titers[291]	Preclinical studies suggest retained neutralizing antibodies[292]	Preclinical studies suggest drastically reduced neutralizing antibodies[117,293]
Moderna COVID-19 Vaccine (mRNA-1273); also called Spikevax	A test-negative case–control study in Ontario suggested 90% protection against infection and 100% infection against severe disease[285]	A test-negative case–control study in Ontario suggested 90% protection against infection and 100% protection against severe disease[285]	Interim results from prospective cohort study showed 86% effectiveness from infection and 96% from hospitalization or death—Delta increased to 54% of circulating strains over the course of study, but stratification of effectiveness not provided[294] Meta-analysis suggests 78% efficacy against infection and 98% efficacy against severe disease/death[279]	Neutralization titers against Omicron 35 times lower but restored with a booster dose[114]
Sputnik V	Preclinical review suggests antibody neutralization is retained[295]	Preclinical review suggests antibody neutralization is retained[295]	A new release purports 90% effectiveness against infection[296] A preprint case–control study suggests 81% protection from hospitalization[297]	A preprint preclinical study suggests 12-fold decrease in neutralizing antibody levels with Sputnik V that is restored with booster of Sputnik Light[160]
CoronaVac	Preclinical studies suggested slightly reduced neutralizing antibody titers[291,298]	Preclinical studies suggested reduced neutralizing antibody titers[291,298]	A test-negative case–control study showed 59% effectiveness against infection and 100% effectiveness against severe	Preclinical studies suggest low level of neutralizing antibodies but partially restored with mRNA booster[301]

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Table 4 (*Continued*)

Name	Alpha (B.1.1.7)	Beta (B.1.351)	Delta (B.1.617.2)	Omicron (B.1.1.529)
	News release purports efficacy against infection[299]	News release purports efficacy against infection[299]	disease[300] Meta-analysis suggests 59% efficacy against infection and 75% efficacy against severe disease/death[279]	
NVX-CoV2373 (Nuvaxovid; Covovax in India)	86–93% protection against infection and 100% protection against severe disease[227,302]	Interim results from phase 2 trial in South Africa suggest reduced efficacy against infection (51%), protection from severe disease, pending final analysis[303]	A news release purports neutralizing antibody titers augmented by booster[304]	A new release purports cross-reactive immune response to Omicron after 2-dose series that increases to wild-type levels of neutralization with a third dose[305]
Sputnik Light	Preclinical data suggest comparable neutralizing antibody titers[228]	Preclinical data suggest slightly reduced neutralizing antibody titers[228]	News release statement of 70% effective against infection increased to 83 and 94% against hospitalization when given booster. Preprint analysis suggests 75% efficacy against infection[306]	A preprint preclinical study suggests a 12-fold decrease in neutralizing antibody levels with Sputnik V that is restored with booster of Sputnik Light[160]
Covaxin (BBV152)	Preprint preclinical study suggests comparable neutralizing antibodies[307]	A preclinical study suggests maintained neutralizing antibodies[308]	Meta-analysis suggests 65% efficacy against infection.[279] A test-negative case–control study suggested 65% efficacy against infection and 93% against severe disease[309]	A news release purports that a preclinical study found high neutralizing antibodies with booster[310]

the variants. As of June 2022, Omicron and it's subvariants (BA.2.12.1, BA.4, and BA.5) are the dominant variants worldwide.[113] Omicron's increased transmissibility led to a global wave of infections prompting concern that it had effectively escaped vaccine-induced immunity. Early data suggest a decrease in neutralizing antibody titer against Omicron.[114–117] Two doses of BNT162b2 or AZD1222 were shown to provide only limited protection (<50%) against symptomatic disease with additional waning over time.[118] However, the vaccines do appear to retain protection against severe disease.[119,120]

Duration of Protection

Initial vaccine efficacy reports at the time of emergency use authorization were based on an average follow-up period of 2 to 3 months. Since then, immunogenicity has been tracked in largely observational studies.[121] All the vaccines with longitudinal follow-up data have shown some degree of waning immunity with time through measured infections or decreased antibody levels (►**Table 5**).[122–141] Although there is certainly heterogeneity between studies, particularly regarding the degree of waning per vaccine, the general trend was captured in a systemic review and meta-regression of the BNT162b2, mRNA-1273, AZD1222, and Ad26.COV2.S vaccines.[131] The analysis suggests that vaccine effectiveness against symptomatic SARS-CoV-2 infection decreased on average 20 to 30 percent in 6 months after full vaccination.[131] However, effectiveness against severe disease remained high, with an average decrease of only 9 to 10 percentage points at 6 months.[131] Data on efficacy over time are confounded by the emergence of new variants but a test-negative case–control study during Delta variant predominance did demonstrate that time since vaccination was an independent factor in waning.[126] There does seem to be variation in waning among individuals. Those with prior infection seem to have what some refer to as "super-immunity" with higher levels of neutralizing antibody and more prolonged protection.[142] Whether this will hold up against future variants is not clear. The data on waning immunogenicity from the remaining vaccines highlighted in ►**Table 5** come largely from preprint and antibody-based studies; the full correlation to the effectiveness of these is unclear at this time.

Booster Vaccines

A booster dose refers to that given after completion of the primary vaccination series (►**Table 6**) to restore vaccine effectiveness after clinical protection has dropped over time below a threshold level of protection. Alternatively, an additional dose of a vaccine refers to the extension to a primary series given to populations (such as the immunocompromised) who were felt to have an insufficient response to the primary series to enhance vaccine effectiveness. Additional doses will be covered under a later section on the immunocompromised.

Boosters were introduced due to concerns for waning vaccine effectiveness and decreased responsiveness of

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Table 5 Duration of protection and booster doses

Name	Duration of protection	Efficacy of booster	Timing and dose recommended for first booster dose
COVID-19 Vaccine AstraZeneca (AZD1222); also known as Vaxzevria and Covishield	Andrews et al 2022[122] • Test negative case control study in England • Time period: 2–9 wk → ≥20 wk • VE against symptomatic disease: 67.6% → 44.3% • VE against hospitalization: 95.2% → 80% Poukka et al 2022[123] • Retrospective cohort study in Finland • Time period: 14–90 d → 91–180 d • VE overall: 89% → 63% Nordström et al 2022[124] • Retrospective cohort study in Sweden • Time period: 15–30 d → ≥121 d • VE overall: 68% → no detectable VE Katikireddi et al 2022[125] • Retrospective cohort study in Brazil/Scotland • Variants: Scotland (delta), Brazil (non-delta) • Time period: 2–3 wk → 18–19 wk • VE overall (Scotland): 83.7% → 63.7% • VE overall (Brazil): 86.4% → 42.2%	• Munro et al 2022 (COV-Boost trial)[144] • Randomized phase 2 controlled trial in the UK • Showed: participants (age >30) given homologous boosting with AZD1222 had augmented antibody and neutralizing responses • Increased cellular response was not demonstrated Flaxman et al 2021[145] • Sub-study of two randomized phase 1/2 (COV001) and 2/3 (COV002) controlled trials • Showed: adults (18–55) given a booster vaccination 28–38 weeks post-primary series had increased antibody titers and T-cell responses	Timing post-primary vaccination: • WHO: 4–6 months • EMA: ≥3 months
Comirnaty (BNT162b2)	Britton et al 2022,[126] Thomas et al 2021,[127] Chemaitelly et al 2021,[128] Lin et al 2022,[129] Young-Xu et al 2021,[130] Andrews et al 2022,[122] Feikin et al 2022[131] • Numerous studies have detailed waning VE overall while maintaining high VE against severe disease • Range of waning overall VE through 6 months: 70–96.2% → 17.9–83.7% • Range of VE against severe disease through 6 months: 89–99% → 55.6–98.4% Feikin et al 2022[131] • Systemic Review/meta regression of 4 vaccines (including 38 BNT162b2 vaccine studies) • Time period: 6 months post full vaccination • Overall VE (4 vaccines combined): decreased 20–30% on average • VE against severe disease: decreased 9–10% on average	Falsey et al 2021,[146] Eliakim-Raz et al 2021,[149] Atmar et al 2021,[148] Munro et al 2021[144] • Several antibody-based studies showed augmented antibody titers by booster vaccination. Spitzer et al 2022,[149] Wald 2022[150] • Prospective cohort study of HCW in Israel • Showed: booster dose was significantly associated with lower rate of SARS-COV-2 infection compared with primary vaccination series alone with relative reduction of 93% (adjusted hazard ratio of 0.07) Bar-On et al 2021[151] • Retrospective cohort study in Israel of individuals >16 years of age fully vaccinated at least 5 months earlier • Showed: booster dose decreased rate of SARS-COV-2 infection by a factor of 10 for all age groups • Booster dose decreased rate of severe illness by factor of 17.9 for individuals ≥60 and 21.7 for pts 40–59 years Andrews et al 2022[152] • Test negative case control study in England • Showed: relative vaccine effectiveness 14–35 days after a booster dose was 82.8% in comparison to VE data from group's prior study of primary series performance at ≥20	Timing post-primary vaccination: • CDC: ≥2 months • WHO: 4–6 months • EMA: 3–6 months Dose: same as primary dose

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Table 5 (*Continued*)

Name	Duration of protection	Efficacy of booster	Timing and dose recommended for first booster dose
		weeks w/o booster of 69.7% • Relative VE against hospitalization in pts ≥50 after booster dose was 98.7%	
COVID-19 Vaccine Janssen (JNJ-78436735; Ad26.COV2.S)	Data are varied with more studies showing trend toward decreased VE with time Lin et al 2022[129] • Retrospective cohort study in North Carolina • Time period: 1 month → 5 months • Overall VE: 74.8% → 59.4% • VE against hospitalization: 85.8% → 81.7% (not statistically significant) Robles-Fontán et al 2022[132] • Retrospective cohort study in Puerto Rico • Time period: 2 wk → 5 months • Overall VE: 64% → 40% • Variants: no difference before and after delta predominance COV3001 interim Follow up data (FDA EUA request 2021)[133] • Phase 3 randomized double-blind placebo-controlled trial • Time period: 14 d → 6 months • VE overall: 66.9% → 56.3% (not statistically significant) • VE severe disease: 76.7% → 73.3% (not statistically significant) Barouch et al 2021[134] • Sub-study of 20 individuals from phase 1/2 clinical trial in Belgium/United States • Time period: 29 d→ 239 d (8 months) • Showed durable humoral and cellular immune responses with minimal decrease at 8 months (median neutralizing antibody titer decreased by factor of 1.8)	Sablerolles et al 2022[153] • Multicenter randomized controlled trial of HCW in the Netherlands • Showed: booster dose resulted in higher S-specific binding antibodies, neutralizing antibodies, and T-cell responses than single-dose primary vaccination • Heterologous booster with mRNA vaccine after primary Ad26.COV2.S vaccination resulted in larger increase in antibody levels than homologous booster dose Atmar et al 2022[148] • Phase 1–2 open label clinical trial in adults who had completed primary vaccination at least 12 weeks prior • Homologous booster w/ Ad26.COV2.S resulted in increased neutralizing antibody titers but not spike specific T-cell responses Oliver et al (MMWR January 2022)[154] • In December 2022, the U.S. Advisory Committee on Immunization Practices made a recommendation for preferential use of mRNA COVID-19 vaccines over the Ad26.COV2.S covid vaccines including for booster doses to pts who had previously received primary Ad26.COV2.S vaccination due to reports of TTS with Ad26.COV2.S vaccination	Timing post-primary vaccination: • CDC: ≥2 months • WHO: not commented on • EMA: ≥ 2 months Dose: same as primary dose Comments: • mRNA booster preferred in most situations (CDC)
BBIBP-CorV/NVSI-06–07	Badano et al 2022[135] • Prospective cohort study of HCW in Argentina • Time period: 20 d→ 90 d • Showed trend toward lower antispike antibody concentrations with time	Yu et al 2022[155] • Prospective cohort study of HCW in China • Showed: booster dose of BBIVP-COV leads to a significant increase in neutralizing immune response against SARS-COV-2 • The Omicron variant showed extensive, albeit incomplete, escape of booster-elicited neutralization (20.1-fold reduction in neutralization titers compared with wild-type strain)	Timing post-primary vaccination: • WHO: 4–6 months Dose: same as primary dose Comments: • Heterologous booster recommended for immunocompromised individuals 3–6 months after third dose (WHO)

(*Continued*)

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Table 5 (*Continued*)

Name	Duration of protection	Efficacy of booster	Timing and dose recommended for first booster dose
		Sinopharm released a recombinant protein vaccine (NVSI-06–07) that was approved for emergency use as a booster in UAE December 2021 Kaabi et al 2022[156] • Randomized phase 2 controlled trial in UAE • Showed heterologous boost w/ NVSI-06–07 to have acceptable safety profile • Showed increased IgG and neutralizing antibody levels w/ both homologous BBIBP-COrV boost and heterologous boost w/ NVSI-0601 but the heterologous boost induced significantly higher immunogenicity including against Omicron	
Moderna COVID-19 Vaccine (mRNA-1273); also called Spikevax	Britton et al 2022,[126] Abu-Raddad et al 2022,[136] Lin et al 2022,[129] Young-Xu et al 2021,[130] Feikin et al 2022[131] • Numerous studies have detailed waning VE overall while maintaining high VE against severe disease • Range of waning overall VE through 6 months: 84–94.1% → 59–92.4% • Range of VE severe disease through 6 months: 89–100% → 85–100% Feikin et al 2022[131] • Systemic review/meta regression of 4 vaccines (including 23 mRNA-1272 vaccine studies) • Time period: 6 months post full vaccination • Overall VE (4 vaccines combined): decreased 20–30% on average • VE against severe disease: decreased 9–10% on average Lin et al 2022[129] • Retrospective cohort study in North Carolina • Time period: 1 month → 7 months • Showed less waning for mRNA-1273 (95.9% → 80.3%) than BNT162b2 (94.5% → 66.6%) although both maintained high VE against severe disease	Atmar et al 2022[148] • Phase 1/2 open label clinical trial in adults who had completed primary vaccination at least 12 wk prior • Showed: increased antibody titers after mRNA-1273 booster dose Thompson et al 2022[157] • Test negative case control study in the United States of adult recipients of an mRNA vaccine (mRNA-1273 or BNT162b2) • Showed: VE against COVID-19-associated hospitalization during Delta and Omicron predominance was 81 and 57% respectively in adults who had completed 2 dose primary series ≥180 days earlier and increased to 94 and 90% respectively in adults who had received booster ≥14 days prior	Timing post-primary vaccination: • CDC: ≥2 months • WHO: 4–6 months • EMA: ≥3 months Dose: half of dose used in primary series
Sputnik V	Chahla et al 2022[137] • Prospective cohort study of HCW in Argentina • Time period: 28 d → 180 d • Showed progressive decrease in anti-SAR-CoV-2-receptor binding domain IgG titers starting at	Under investigation. See Sputnik Light	Timing post-primary vaccination: • Bahrain: ≥6 months (press release –Bahrain News Agency September 2021)[180] Dose: same as primary dose Age: ≥18 years

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Table 5 (*Continued*)

Name	Duration of protection	Efficacy of booster	Timing and dose recommended for first booster dose
	d60 (94% participants with detectable titers at d90 → 31% with detectable titers at d180)		
CoronaVac	Xu et al 2021[138] • Prospective cohort study in China • Time period: 14 d → 160 d • Showed decrease in neutralizing antibody levels with time (149 IU/mL t → 14.23 IU/mL) Suah et al[141] • Retrospective cohort study in Malaysia • Time period: 3 months → 5 months • Overall VE: 74.4% → 30% • VE against ICU admission: 56.1% → 29.9% • VE against death: significant waning not observed	Costa Clemens et al 2022[158] • Phase 4 randomized single-blind trial in Brazil of adults 6 months after completion of primary series • Showed: booster dose of CoronaVac increased IgG antibody levels when measured at day 28 post booster • Heterologous booster doses given after CoronaVac primary series, had higher anti-spike IgG levels at day 28 than homologous booster • Pseudo-virus neutralizing antibodies had 100% seropositivity for all groups tested as part of heterologous boosting compared with only 66.7% seropositivity in older adults (>60) w/ homologous boosting	Timing post-primary vaccination: • WHO: 3–6 months (for pts ≥ 60 years) • WHO: not commented on for age <60 years Dose: dame as primary series
NVX-CoV2373 (Nuvaxovid; Covovax in India)	Press release by Novavax (February 2022)[139] • Interim update to phase 3 trial data • Time period: 3 → 6 months • Overall VE: 89.7% → 82.7% (not statistically significant) • VE against severe disease: remained high at 100%	Mallory et al 2021[159] • Phase 2 trial of adults aged 18–84 in the United States and Australia given a booster dose 6 months after completion of primary series • Showed: neutralizing antibody increased 4.1-fold after booster dose	Timing post-primary vaccination: • WHO/EMA: not commented on Dose: same as primary dose
Sputnik Light	Remains under investigation, no clinical published data available yet	Dolzihikova et al 2021 (preprint)[160] • Retrospective cohort study of individuals who completed primary vaccination w/ Sputnik and then were boosted with Sputnik Light • Showed: boosted individuals had a smaller decrease in level of neutralizing antibodies (7.13-fold) than vaccination w/ Sputnik V alone (11.76-fold) and despite decrease, all boosted individuals maintained detectable neutralizing antibody in sera to Omicron variant	Timing post-primary vaccination: • Not commented on Dose: same as primary dose
Covaxin (BBV152)	Choudhary et al 2021[140] • Prospective cohort study of HCW in India • Time period: 1 month → 6 months • Showed 4-fold decrease in vaccine-induced spike antibody titers	Edara et al 2022 (preprint)[161] • Phase 2 trial amended to include booster doses of Covaxin, evaluated sera 28 days post booster administration • Showed: 100% of Covaxin boosted individuals had neutralizing activity against delta variant and 90% had neutralizing activity against Omicron variant	Timing post-primary vaccination: • WHO: 4–6 months Dose: same as primary dose

Abbreviations: CDC, Centers for Disease Control and Prevention; EMA, European Medicines Agency; FDA, Food and Drug Administration; WHO, World Health Organization.
Note: COVID-19 pandemic is ongoing, information here is subject to change with new data and as new variants emerge.

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Table 6 Current recommended dosing of primary series of COVID-19 vaccines

Name	Dose per U.S. FDA/CDC[167,169]	Dose per European guidelines (EMA)[166,168,171,175,311,312]	Dose per WHO[165,170,172–174,176–179,313,314]	Additional Individual country data
COVID-19 Vaccine AstraZeneca (AZD1222); also known as Vaxzevria and Covishield	N/A	Primary series: 2 doses ■ Time between doses: 4–12 wk ■ Age ≥ 18: 0.5 mL (5×10^{10} viral particles) Additional dose (immunocompromised): ■ not commented on	Primary series: 2 doses ■ Time between doses: 8–12 wk ■ Age ≥ 18: 0.5 mL (5×10^{10} viral particles) Additional dose (immunocompromised): ■ Age ≥ 18: 1–3 months after second dose	
Comirnaty (BNT162b2)	Primary series (age >5): 2 doses ■ Time between doses: 3–8 wk ■ Age ≥ 12: 0.3 mL (30 μg) ■ Age 5–11: 0.2 mL (10 μg) ■ Age 6 months –4 years: 0.2mL (3 μg) Additional dose (immunocompromised): ■ Age ≥ 5: 1 month after second dose	Primary series: 2 doses ■ Time between doses: 3 wk ■ Age ≥ 12: 0.3 mL (30 μg) ■ Age 5–11: 0.2 mL (10 μg) Additional dose (immunocompromised): ■ Age ≥ 5: 1 month after second dose	Primary series: 2 doses ■ Time between doses: 4–8 wk (preference given to 8 wk for lower myocarditis/pericarditis risk) ■ Age ≥ 12: 0.3 mL (30 μg) ■ Age 5–11: 0.2 mL (10 μg) Additional dose (immunocompromised): ■ Age ≥ 5: 1–3 months after second dose	
COVID-19 Vaccine Janssen (JNJ-78436735; Ad26.COV2.S)	Primary series: 1 dose ■ Age ≥ 18: 0.5 mL (5×10^{10} viral particles) Additional dose (immunocompromised): ■ Age ≥ 18: 1 month after 1st dose w/ an mRNA vaccine	Primary series: 1 dose ■ Age ≥ 18: 0.5 mL (5×10^{10} viral particles) Additional dose (immunocompromised): ■ Not commented on	Primary series: countries can choose 1 or 2 dose series ■ Time between doses: 2–6 mo ■ Age ≥ 18: 0.5 mL (5×10^{10} viral particles) Additional (second) dose (immunocompromised): ■ Age ≥ 18: 1–3 months after first dose	
BBIBP-CorV/NVSI-06–07	N/A	N/A	Primary series: 2 doses ■ Time between doses: 3–4 wk ■ Age ≥ 18: 0.5 mL (4 μg) Additional dose (immunocompromised): ■ Age ≥ 18: 1–3 months after second dose	
Moderna COVID-19 Vaccine (mRNA-1273); also called Spikevax	Primary series: 2 doses ■ Time between doses: 4–8 wk ■ Age ≥ 12: 0.5 mL (100 μg) ■ Age 6–11: 0.5 mL (50 μg) ■ Age 6 mo–5 y: 0.25 mL (25 μg) Additional dose (immunocompromised): ■ Age ≥ 18: 1 month after second dose	Primary series: 2 doses ■ Time between doses: 1 month ■ Age ≥ 12: 0.5 mL (100 μg) ■ Age 6–11: 0.25 mL (50 μg) Additional dose (immunocompromised): ■ Age ≥ 6: 1 month after second dose	Primary series: 2 doses ■ Time between doses: 4–8 weeks (preference given to 8 wk for lower myocarditis risk) ■ Age ≥ 12: 0.5 mL (100 μg) Additional dose (immunocompromised): ■ Age ≥ 12: 1–3 months after second dose	

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Table 6 (*Continued*)

Name	Dose per U.S. FDA/CDC[167,169]	Dose per European guidelines (EMA)[166,168,171,175,311,312]	Dose per WHO[165,170,172–174,176–179,313,314]	Additional Individual country data
Sputnik V	N/A	N/A	WHO Evaluation for Authorization in process	Primary series: 1 dose ■ Age ≥ 18: 0.5 mL (10^{11} viral particles; Logunov et al)[25] Additional dose (immunocompromised): ■ Not commented on
CoronaVac	N/A	N/A	Primary series: 2 doses ■ Time between doses: 4 wk (in contrast to 2–4 wk in manufacturing label) ■ Age ≥ 18: 0.5 mL (3 µg) Additional dose (immunocompromised): ■ Age ≥ 18: 1–3 months after second dose	
NVX-CoV2373 (Nuvaxovid; Covovax in India)	N/A	Primary series: 2 doses ■ Time between doses: 3 wk ■ Age ≥ 18: 0.5 mL (0.5 µg spike protein–50 µg adjuvant matrix M) Additional dose (immunocompromised): ■ not commented on	Primary series: 2 doses ■ Time between doses: 3–4 wk ■ Age ≥ 18: 0.5 mL (0.5 µg spike protein–50 µg adjuvant matrix M) Additional dose (immunocompromised): ■ Age ≥ 18: 1–3 months after second dose	
Sputnik Light	N/A	N/A	WHO Evaluation for Authorization in process	Primary series: 1 dose ■ Age ≥ 18: 0.5 mL (10^{11} viral particles; Tukhvatulin et al)[228] Additional dose (immunocompromised): ■ not commented on
Covaxin (BBV152)	N/A	N/A	Primary series: 2 doses ■ Time between doses: 4 wk ■ Age ≥ 18: 0.5 mL (6 µg) Additional dose (immunocompromised): ■ Age ≥ 18: 1–3 months after second dose	

Abbreviations: CDC, Centers for Disease Control and Prevention; EMA, European Medicines Agency; FDA, Food and Drug Administration; N/A, not applicable; WHO, World Health Organization.
Note: COVID-19 pandemic is ongoing, information here is subject to change with new data and as new variants emerge.

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vaccines to variants. By the end of 2021, at least 126 countries had issued recommendations on booster doses and 120 countries had begun implementation.[143]

Immunogenicity and Effectiveness of Boosters

Booster doses have been shown to both augment immune response through restoration of neutralizing antibody titers and, for those in which it has been studied (largest data pool from observational studies of mRNA-1273 and BNT162b2 during Delta and Omicron variant predominance), to increase vaccine effectiveness both against symptomatic COVID-19 and severe disease (►**Table 5**).[144–161] No significant safety concerns have been identified in these trials evaluating boosters or in postmarketing surveillance data.[162]

Homologous versus Heterologous Boosters

Some of the most robust data evaluating immunogenicity or effectiveness of boosters come from mixing and matching studies that looked at homologous boosters (same vaccine as primary series) versus heterologous boosters (different vaccine than primary series). COV-Boost was a multicenter randomized phase 2 trial of safety and immunogenicity of various homologous and heterologous boosters given after primary AZD1222 or BNT162b2 vaccination among 2,878 participants over age 30 in the United Kingdom.[144] AZD1222, BNT162b2, mRNA-1273, and Ad26.COV2.S were all tested as boosters and found to increase antibody and neutralizing responses after both AZD1222 and BNT162b2 primary vaccination with no significant safety concerns.[144] Similarly, a phase 1 to 2 open label multicenter clinical trial of 458 adults in the United States who had received a primary vaccination series with mRNA-1273, BNT162b2, or Ad26.COV2.S evaluated immunogenicity after boosting by one of these three vaccines.[148] In all vaccine combinations, antibody-neutralizing titers and binding titers increased after boosting. Heterologous boosters increased neutralizing titers by a factor of 6 to 73 versus homologous boosters increased titers by a factor of 4 to 20. Although not designed to compare booster regiments, heterologous mRNA boosters (meaning an mRNA vaccine given after Ad26.COV2.S or a different mRNA primary vaccination) generally produced the greatest increase in neutralizing antibody titers for each primary vaccine category.[148,153] In addition, a phase 4 randomized single-blind trial of 1,240 adults in Brazil who had completed a primary vaccination series with CoronaVac showed that heterologous boosting with AZD1222, BNT162b2, or Ad26.COV2.S induced higher neutralizing antibody levels than homologous boosting.[158]

Similar trends have been observed in studies of clinical effectiveness. A retrospective matched cohort study of 4,806,026 U.S. Veterans primed with mRNA-1273, BNT162b2, or Ad26.COV.2.S vaccines showed that in the Ad26.COV.2.S primed vaccine cohort, the incidence of infection after a heterologous booster dose was approximately 50% lower than after homologous booster (adjusted rate ratio 0.49).[163] Adjusted rate ratios for moderate and severe/critical disease were also lower after heterologous boosting. In this study, no statistically significant difference was found between heterologous and homologous boosting among the individuals who had received an mRNA primary vaccine series.[163] This contrasts with a retrospective cohort study of 576,132 adults aged 60 and older in Singapore who completed primary vaccination series with BNT162b2 or mRNA-1273, which showed individuals who received heterologous mRNA boosting had lower incidence of SARS-COV-2 infection than those who received homologous mRNA boosting.[164]

Timing to Booster

The decision on timing to booster dose has been individualized by each country's health administration based on vaccine supply, baseline vaccine effectiveness, data on specific vaccine waning, and emergence of variants. Implementation per country generally began with booster vaccination of the most vulnerable populations such as the elderly and immunocompromised with subsequent expansion to rest of the population as supply allowed. For the majority of vaccines, a booster is recommended at an interval of 4 to 6 months per WHO (►**Table 5**).[165–180] The WHO does not comment on AD26.COV2.S timing to booster, but the U.S. Centers for Disease Control and Prevention (CDC) and the EMA advise dosing at 2 months post-primary vaccination based on lower baseline vaccine effectiveness compared with mRNA vaccines authorized in these countries.[167,169,171]

Waning of Boosters

It is difficult to predict how long the enhanced immunogenicity or clinical effectiveness of boosters will last or how they will hold up against future variants. In the VISION NETWORK study of mRNA vaccines in the United States, vaccine effectives against COVID-19-associated hospitalization decreased from 91 to 78% four plus months after a booster.[181] This observed waning led to investigations into the utility of a second booster dose. An 8-week observational cohort study in Israel of individuals aged 60 and above showed that a fourth dose of BNT162b2 reduced rates of confirmed SARS-COV-2 infection overall by a factor of 2 and the rate of severe disease by a factor of 3.[182] The protection against severe disease was sustained during the study period but protection against infection overall waned quickly.[182] This data, along with industry proprietary data and the VISION NETWORK study prompted the United States as well as other countries to offer a second booster to the elderly and immunocompromised (discussed further below).[183–185]

Special Populations

Immunocompromised Individuals

Many conditions can compromise an individual's immune system and effect their ability to mount an appropriate immunological response to a COVID-19 vaccine. For this reason, the WHO, CDC, and EMA recommend extending the primary COVID-19 vaccine series with an additional dose for individuals who are moderately or severely immunocompromised (see ►**Table 7** for a list of qualifying conditions).[167] As immunocompromised hosts are also

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Table 7 Moderately and severely immunocompromising conditions include the following[167]

- Active use of chemotherapy for cancer
- Hematologic malignancies
- History of stem cell transplant within 2 years
- History of solid organ transplant on immune-suppressive medications
- Moderate or severe primary immunodeficiency syndrome (such as Wiskott–Aldrich syndrome)
- Advanced or untreated HIV (CD4 count <200)
- Receiving high-dose corticosteroids or other immune-suppressive medications.[167]

Abbreviation: HIV, human immunodeficiency virus.
Note: This list is not exhaustive and additional conditions can be considered on individual basis in discussion with patient's care team.

subject to waning immunity, one to two booster doses are recommended in this population post extended primary series.[167]

Evidence on Lower Immunogenicity

Lower immunogenicity or vaccine effectiveness after primary vaccination series in immunocompromised patients has been demonstrated in multiple observational studies and clinical trials, most extensively studied with mRNA vaccines.[186] The degree of reduced immunogenicity varies by type of immunocompromised condition as seen in the COVICS prospective cohort study of 1,271 adults (including 1,099 immunocompromised hosts) who had completed a primary vaccination series 2 to 5 months prior with mRNA-1273 (614 participants), BNT162b2 (644), Ad26.COV2.S (11), or AZD1222 (2).[187] Seropositivity, as measured by IgG to SARS-CoV-2 RBD, was significantly lower at 30.7% amongst adults with history of solid organ transplant (SOT), compared with 92.4% in health care workers that served as controls.[187] Vaccination within 1 year of SOT and administration of two or more immunosuppressive medications were independently associated with lower odds of seropositivity.[187] Lower seropositivity was also observed in hematological malignancies (50.0%), in autoimmune conditions (79.1%), in patients with solid tumors (78.7%), and in persons living with human immunodeficiency virus (79.8%) where specifically CD4 count <200 was associated with lower odds of seropositivity.[187] Additional factors found to be associated with poor antibody response in a systemic review of SOT patients included older age, deceased donor status, antimetabolite use, and recent antithymocyte globulin exposure.[188] Use of anti-CD20 monoclonal antibody therapy has also been associated with lower vaccine responsiveness, as measured by antibody levels, in patients with lymphoid malignancies.[189]

Evidence on Safety of Additional Dose

Safety data overall demonstrate similar results to additional doses as was observed in primary vaccination series.[186] In a randomized trial of 120 SOT recipients, a third dose of mRNA-1273 vaccine was found to have an overall positive safety profile.[190] No grade 3 or 4 events were observed, and no cases of acute rejection occurred.[190]

Evidence on Benefit of Additional Doses

A case–control study of 2,952 adults (1,077 immunocompromised) in the United States demonstrated that vaccine efficacy against COVID-19 hospitalization was higher among immunocompromised adults who had received three doses (88%) of an mRNA vaccine than those who had received two doses (69%).[191] In a systemic review of 11,713 SOT recipients, the mean seroconversion rate to antispike antibodies after mRNA vaccine improved with subsequent doses (10.4% after 1 dose, 44.9% after 2 doses, and 63.1% after 3 doses) but remained lower than nonimmunocompromised hosts.[188] The optimal number of doses of vaccine in the immunocompromised remains under investigation and recommendations vary by health organization with several countries advising two boosters after primary series as summarized in ►**Table 5**.[167,192]

Additional Considerations in Immunocompromised Individuals

Given the effect of immunosuppressive medications on vaccine immunogenicity, several organizations provide guidance on timing of therapy and vaccination. The CDC recommends that if disease state allows, COVID-19 vaccines should be given at least 2 weeks before initiation or administration of immunosuppressive medications.[167] There is variation by condition and expert consultation can be of assistance in determining optimum timing. In addition, for individuals who undergo hematopoietic stem cell transplant or CAR T-cell (chimeric antigen receptor T-cell) therapy, revaccination with full primary series and boosters is recommended starting 3 months after transplant/CAR-T-cell therapy.[167] While vaccination remains crucial, additional mitigation strategies are also needed to reduce the risk to the immunocompromised including vaccination of close contacts and consideration of monoclonal antibody prophylaxis.

Pregnant Women

COVID-19 in pregnancy has been associated with significant increases in severe maternal morbidity and mortality as well as neonatal complications.[193] For this reason, the WHO recognizes pregnant individuals as a priority group for vaccination. A large prospective cohort study of pregnant individuals in Scotland showed that vaccination against COVID-19 (with BNT162b2, mRNA-1273, or AZD1222) was associated with improved outcomes in the setting of SARS-COV-2 positivity.[194] They found that 77.4% of SARS-COV-2 infections, 90.9% of SARS-COV-2-associated hospital admissions, and 98% of SARS-COV-2 critical care admissions occurred in unvaccinated individuals.[194] Vaccination of pregnant individuals has also been found to confer a benefit to their infants. In a test-negative case–control study of 379 infants in the United States, maternal receipt of two doses of an mRNA vaccine during pregnancy had a 61% protection against COVID-19-associated hospitalization in infants up to 6 months.[195]

Although pregnant women were excluded from the initial large clinical trials of COVID-19 vaccines, no significant safety concerns have been identified in this population to

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Table 8 Safety data of vaccines in pregnancy

Animal studies	■ Developmental and reproductive toxicology animal studies were completed for all of the vaccines under WHO EUL (BNT162b2, MRNA-1273, AZD1222, AD26.COV2.S, Sinopharm BIBP, Sinovac-Coronavac, BBV152, NVX-Co2373)[196] ■ No harmful effects of vaccination to pregnant animals or their offspring were found[196]
Epidemiological monitoring data	Pregnant women have also been monitored in epidemiological studies postvaccination with no unique safety concerns identified. ■ mRNA vaccine safety surveillance studies in the United States showed no increased rate of spontaneous abortion in vaccinated pregnant individuals[197,315] ■ Large retrospective cohort studies have been conducted in Canada, the United States, the United Kingdom, Sweden, and Norway and showed COVID-19 vaccination was not associated with increased risk of postpartum hemorrhage, chorioamnionitis, cesarean delivery, preterm birth, still birth, admission to neonatal intensive care unit, small for gestational age, or low Apgar score[198–201] ■ Although individuals in these studies predominantly received mRNA vaccines, one of the U.S.-based studies contained 424 individuals who had been vaccinated with Ad26.COV2.S and UK COVID vaccine surveillance data contained 5,319 individuals giving birth who had received one or more doses of AZD1222 as of February 2022[199,201] ■ A preprint observational study from Brazil also included 2,016 individuals who had received AZD1222, 123 who had received CoronaVac, and 56 who had received Ad26.COV2.S and showed no increased adverse events including rate of spontaneous abortion in vaccinated pregnant individuals compared with reported rates in nonpregnant individuals[202] ■ In a surveillance data from India, 120,000 pregnant individuals had received the BBV152 vaccine as of October 2021 and only minor adverse events related to the vaccine have been reported. However, neonatal specific outcomes have not yet been collected[179]
Insight from how the vaccines work	• None of the vaccines contain live virus and therefore do not cause COVID-19 • Several of the vaccine components including those in AZD1222, Ad26COV2.S, BIBP, and CoronaVac have been used in other non-COVID-19 vaccines during pregnancy without safety concerns[196]

date. None of the COVID-19 vaccines highlighted here contain replication-competent virus and therefore do not cause COVID-19 to pregnant individuals or fetuses. Developmental and reproductive toxicology animal studies were completed for all the vaccines under WHO Emergency Use Listing (EUL).[196] No harmful effects of vaccination to pregnant animals or their offspring were found. Pregnant women have also been monitored in epidemiological studies post-vaccination with no unique pregnancy-related safety concerns identified (see ►**Table 8**).[179,196–202]

There are no unique vaccine scheduling parameters for pregnant individuals. Vaccination is recommended as soon as feasible without regard to gestational age and the interval between primary series and booster doses is the same as advised for nonpregnant individuals.

Pediatrics

Although the initial COVID-19 vaccine trials were focused on adults, multiple studies have now been conducted in the pediatric population and additional studies are ongoing. Thus far, clinical trials and postmarketing surveillance studies have shown that the COVID-19 vaccines studied in children to have overall high efficacy and effectiveness and to have an acceptable safety profile.[203–210] Based on these accumulating data, the WHO has issued an EUL for two vaccines in children (BNTb162b for individuals greater than age 5 and mRNA-1273 for age greater than age 12) and numerous countries have given authorization for pediatric vaccination for children as young as 6 months (see ►**Table 6**).[165–168,170,210,211]

Children and adolescents are overall less likely to get severely ill from COVID-19 than adults.[212] WHO data from December 2019 to October 2021 revealed that children less than 5 made up 2% of reported global cases and 0.1% of reported global deaths, those 5 to 14 years old made up 7% of reported cases and 0.1% of deaths, and those 15–24 years old made up 15% of reported cases and 0.4% of deaths.[210] WHO advises prioritization of vaccination of the highest risk populations first in the setting of limited vaccine supply, which means taking into consideration that a larger burden of severe disease is in adults. They acknowledge that risk–benefit ratio favors vaccination of individuals of all ages but that the direct benefit of vaccinating children is less than adults. Reasons to vaccinate children beyond case reduction include decreasing the incidence of AEs of COVID-19 in children including post-COVID-19 sequelae and hyper-inflammatory syndrome (called multisystem inflammatory syndrome in children [MIS-C] in the United States and pediatric inflammatory multisystem syndrome temporally associated with SARS-COV-2 [PIMS-TS] in Europe). Additional benefits include minimizing household transmission of COVID-19 and minimizing disruption to education from quarantine days.[213]

Conclusions and Future Directions

The speed at which COVID-19 vaccines have been developed is unprecedented and has made a significant impact on the pandemic. Additional vaccines continue to be under investigation, some with novel mechanisms, including a DNA-based vaccine,[214] a spike protein ferritin nanoparticle vaccine, and intranasal vaccines.[27] A multipeptide-

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based vaccine in combination with a toll-like receptor ligand has also been developed called COVAC-1.[215] It is designed to illicit T-cell response in individuals with congenital or acquired B cell deficiencies who do not respond well to the current vaccine platforms. In addition, variant-specific vaccines are being investigated. Although remarkable progress has been made in the development of vaccines and implementation of vaccination campaigns, there is still much work to be done. In addition, the future of COVID-19 vaccines includes several uncertainties including the necessity of continued boosters, the optimal correlates of protection with further investigation needed on the role of humoral versus cellular immunity, and the effect of future variants.

Authors' Contributions
A.A.S. and A.H.B. wrote the initial draft of the manuscript. S.N. and J.V.C. supervised creation of the manuscript and reviewed and edited the manuscript. A.A.S. created the illustrations. All authors reviewed and approved the final draft of the manuscript.

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None declared.

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