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INSIGHTS FROM
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SOCIETY OF INFECTIOUS
DISEASES PHARMACISTS

Early clinical trial data and real-world assessment of COVID-19 vaccines: Insights from the Society of Infectious Diseases Pharmacists

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Abstract

As of August 2021, there were three COVID-19 vaccines available in the United States for the prevention of coronavirus 2019 (COVID-19). The purpose of this narrative review is to examine the early experience from the Emergency Use Authorization (EUA) of BNT162b2 (Pfizer, Inc./BioNTech), mRNA-1273 (Moderna, Inc.), and Ad26.COV2.S (Johnson and Johnson/Janssen Global Services, LLC) through July 2021. The EUA data from the clinical trials have largely been corroborated by real-world effectiveness investigations post-authorization. These studies indicate that immunity is obtained within 2 weeks post-vaccination and may endure for 6 months. The immunity conferred by the vaccines may also be effective against SARS-CoV-2 variants of concern. Additionally, populations not included in the emergency use authorization studies may also benefit from vaccination. This look back at the initial clinical experience can be used by the global community to inform and develop COVID-19 vaccine programs.

KEYWORDS
COVID-19, SARS-CoV-2, vaccines

1 | INTRODUCTION

As of August 2021, there are three vaccines available in the United States for the prevention of coronavirus disease 2019 (COVID-19), the pandemic caused by severe acute respiratory syndrome virus 2 (SARS-CoV-2), BNT162b2 (Pfizer, Inc./BioNTech), mRNA-1273 (Moderna, Inc.), and Ad26.COV2.S (Johnson and Johnson/Janssen Global Services, LLC). These vaccines have the potential to dramatically reduce the number of COVID-19 cases and end the pandemic. Prior to their introduction into clinical practice, these vaccines

underwent rigorous evaluation at the preclinical and clinical level. In the first months of their use in clinical practice, numerous studies have augmented our understanding of the safety and effectiveness of these agents. The purpose of this review is to summarize the approval process, clinical trial data, and early real-world experience with the COVID-19 vaccines currently authorized for use in the United States. It is important to note that this review is written in the context of vaccines available in the United States and that other vaccine products exist in other countries or may become available at a later date.

TABLE 1 Late-stage clinical trials of COVID-19 vaccines (BNT162b2, mRNA-1273, and Ad26.COV2.S) with emergency use authorization

Vaccine	Time and locations	Study design	Key inclusion criteria	Key exclusion criteria
BNT162b2 mRNA COVID-19 Vaccine (BioNTech and Pfizer)[4]	• July 27, 2020–November 14, 2020 • First data cutoff October 9, 2020 • 152 sites worldwide	• Phase 2/3 • Randomized (1:1), placebo-controlled, observer-blinded • N = 43,448	• Age 16–85 years • Healthy as judged by medical history, physical examination, and clinical judgment of investigator	• Immunosuppressive therapy • Immunocompromising condition (HIV, HCV, and HBV) • Persons who were pregnant or breastfeeding • History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s)
mRNA-1273 SARS-CoV-2 Vaccine (Moderna) (COVE study)[5]	• July 27, 2020–October 23, 2020 • 99 sites across the US	• Phase 3 • Randomized (1:1), placebo-controlled, observer-blinded • N = 30,420	• Age ≥ 18 years • No history of SARS-CoV-2 • Persons deemed high risk of SARS-CoV-2 • Healthy/stable chronic medical conditions	• Acutely ill or febrile 72 h prior to screening • Persons who were pregnant or breastfeeding • Known history of SARS-CoV-2 • Allergy, anaphylaxis, urticaria, or other significant adverse reaction to the vaccine or its excipients • Certain bleeding disorders • Non-study vaccine requiring separation from COVID-19 vaccine • Immunosuppressive or immunodeficient state, asplenia, recurrent severe infections • Systemic immunosuppressants or immune-modifying drugs for >14 days within 6 months • Immunoglobulin or blood products in the past 3 months • Donated ≥450 ml of blood products within past 28 days
Ad26.COV2.S COVID-19 Vaccine (Johnson & Johnson) (ENSEMBLE study)[6]	• September 21, 2020–January 22, 2021 • 8 countries worldwide	• Phase 3 • Randomized (1:1), double-blind, placebo-controlled • N = 39,321	• Age ≥18 years • Good/stable health	• Significant acute illness • Temperature ≥38.0 C • Allergy or anaphylaxis or other serious adverse reaction to vaccines or excipients • Abnormal function of immune system • Receipt or planning to receive intravenous immunoglobulin within previous 3 months or blood products in the 4 months before study • Persons who were pregnant or breastfeeding • Coexisting conditions that increased risk of severe COVID-19

Abbreviations: P, placebo; RT-PCR, reverse transcriptase-polymerase chain reaction; V, vaccine; VE, vaccine efficacy.

[a]Fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhea, or vomiting, combined with a respiratory specimen obtained during the symptomatic period (or within 4 days before or after symptoms) that was positive for SARS-CoV-2 by nucleic acid amplification-based testing, either at the central laboratory or at a local testing facility (using a protocol-defined acceptable test).

[b]Calculated from EUA materials.

[c] At least two of the following symptoms: fever (temperature ≥38°C), chills, myalgia, headache, sore throat, or new olfactory or taste disorder, or as occurring in those who had at least one respiratory sign or symptom and at least one nasopharyngeal swab, nasal swab, or saliva sample (or respiratory sample, if the participant was hospitalized) that was positive for SARS-CoV-2 by reverse transcriptase-polymerase chain reaction (RT-PCR) test.

[d] Measured within 7 days of intramuscular injection. From VRBPAC data.

[e] Mild COVID-19 defined as a SARS-CoV-2-positive RT-PCR or molecular test result from any available respiratory tract sample (eg, nasal swab sample, sputum sample, throat swab sample, saliva sample) or other sample AND One of the following symptoms: fever, sore throat, malaise, headache, myalgia, gastrointestinal symptoms, cough, chest congestion, runny nose, wheezing, skin rash, eye irritation or discharge, or chills, without shortness of breath or dyspnea. Moderate COVID defined as positive SARS-CoV-2 test as above AND any 1 new or worsening sign AND any new or worsening symptom. Severe/critical COVID-19 defined as positive SARS-CoV-2 test as above AND clinical signs at rest indicative of severe systemic illness, respiratory failure, evidence of shock, significant acute renal, hepatic, or neurologic dysfunction, admission to the ICU, or death.

[f] Calculated from EUA materials.

Study population	Outcomes		Safety
	Efficacy		

• Female: 49%
• White: 83%
• Black: 9%
• Hispanic/Latinx: 28%
• Median age: 52 years (42% >55 years)
	• Primary Efficacy Outcome: COVID-19[a] at least 7 days after second injection in those without prior history of infection and those with and without prior history of infection
	• Without prior evidence of infection:
	  o Vaccine: 8 cases in 2214 person-years
	  o Placebo: 162 cases in 2222 person-years
	  o VE: 95.0% (90.3–97.6)
	• With and without prior evidence of infection
	  o Vaccine: 9 cases in 2332 person-years
	  o Placebo: 169 cases in 2345 person-years
	  o VE (95% CI): 94.6% (89.9–97.3)
	• Severe COVID-19 after Dose 1
	  o Vaccine: 1/21,669
	  o Placebo: 9/21,686
	  o VE (95% CI): 88.9 (20.1, 99.7)
	• No COVID-19-associated deaths observed
			Local adverse events (V vs. P)[b]
			• Dose 1
			  o Pain: 78% vs. 12%
			  o Redness: 5% vs. 1%
			  o Swelling: 6% vs. 1%
			• Dose 2
			  o Pain: 73% vs. 10%
			  o Redness: 6% vs. 1%
			  o Swelling: 7% vs. 0%
			Systemic Adverse Events (V vs. P)
			• Dose 1
			  o Fever: 3% vs. 1%
			  o Fatigue: 42% vs. 29%
			  o Headache: 35% vs. 27%
			• Dose 2
			  o Fever: 16% vs. 1%
			  o Fatigue: 59% vs. 23%
			  o Headache: 52% vs. 24%

• Female: 47%
• White: 79%
• Black: 10%
• Hispanic/latinx: 21%
• Median age: 51 years (25% >65 years)
	• Primary efficacy outcome: COVID-19 at least 14 days after the second injection in participants who had not previously been infected with SARS-CoV-2
	  o Vaccine: 3.3 per 1000 person-years
	  o Placebo: 56.5 cases per 1000 person-years
	  o VE (95 CI%): 94.1% (89.3–96.8%)
	• Severe COVID-19 starting 14 days after second injection:
	  o Vaccine: 0/14,134
	  o Placebo: 30/14,073
	  o VE (95% CI) based on hazard ratio: 1.00 (NE – 1.00)
	• Severe COVID-19 starting 14 days after second injection:
	  o Vaccine: 0/14,134
	  o Placebo: 30/14,073
	  o VE (95% CI) based on hazard ratio: 1.00 (NE – 1.00)
	• Death
	  o Vaccine: 2 (one from cardiopulmonary arrest and one by suicide)
	  o Placebo: 3 (one from intraabdominal perforation, one from cardiopulmonary arrest, and one from severe systemic inflammatory syndrome in a participant with chronic lymphocytic leukemia and diffuse bullous rash)
			Local adverse events (V vs. P)[d]
			• Dose 1
			  o Pain: 84% vs. 18%
			  o Redness: 3% vs. 0%
			  o Swelling: 6% vs. 0%
			• Dose 2
			  o Pain: 88% vs. 17%
			  o Redness: 9% vs. 0%
			  o Swelling: 12% vs. 0%
			Systemic adverse events (V vs. P)
			• Dose 1
			  o Fever: 1% vs. 0%
			  o Fatigue: 37% vs. 27%
			  o Headache: 33% vs. 27%
			• Dose 2
			  o Fever: 16% vs. 0%
			  o Fatigue: 65% vs. 23%
			  o Headache: 59% vs. 23%

• Female: 45%
• White: 58%
• Black: 19%
• Hispanic/Latino: 6%
• Median age: 52 years (34% >60 years)
	• Primary Efficacy Outcome: Moderate to severe-critical COVID-19 at least 14 days after single dose of vaccine[e]
	  o Vaccine: 116 cases in 3116.6 person-years
	  o Placebo: 348 cases in 3096.1 person-years
	  o VE (95% CI): 66.9% (59.0–73.4%)
	• Death
	  o Vaccine: 3 (none COVID-19 related)
	  o Placebo: 16 (5 COVID-19 related)
			Local adverse events (V vs. P)[f]
			• Pain: 40% vs. 15%
			• Redness: 6% vs. 10%
			• Swelling: 4% vs. 3%
			Systemic adverse events (V vs. P)
			• Fever: 7% vs. 0%
			• Fatigue: 31% vs. 18%
			• Headache: 32% vs. 20%

2 | EMERGENCY USE AUTHORIZATION PROCESS

Prior to being available for routine clinical use, BNT162b2, mRNA-1273, and Ad26.COV2.S, each underwent review by the United States Food and Drug Administration (FDA) using the Emergency Use Authorization (EUA) mechanism. If a drug receives an EUA, the FDA may allow the use of unapproved medical products, such as the COVID-19 vaccine, if certain criteria are met which include no adequate, approved, and available alternatives.[1]

Specific to vaccine EUA, all safety data collected from phase 1 and 2 vaccine studies must be submitted and safety data from phase 3 studies must include a minimum of 2-month follow-up data for at least half of the study population.[1] Furthermore, at least 3000 vaccine recipients must be followed for at least 1 month after completion of the full vaccine schedule to assess all clinical and serious adverse events. In addition to demonstrating efficacy, the point estimate for efficacy must be ≥50% and the lower-bound of the appropriately adjusted confidence interval must be >30%.[2]

While the review is being performed, the FDA holds a public meeting with the Vaccines and Related Biological Products Advisory Committee (VRBPAC) to discuss safety and efficacy and provide the public and scientific communities with data on whether to authorize a vaccine for EUA. Unlike the full FDA approval process which requires extensive data for approval based on preclinical, Phase 1, Phase 2, and Phase 3 clinical trials, an EUA is granted using the best available evidence during an emergency period of time. EUAs allow immediate access to a given therapy with the caveat that an EUA can be revised or revoked based on future safety or efficacy data. In the case of BNT162b2, mRNA-1273, and Ad26.COV2.S, each EUA was based on preclinical through Phase 3 data (see Clinical Trial Data).

It is critically important for clinicians to be able to articulate the difference between EUA and full FDA approval to patients because lack of understanding within the general public may be a considerable source of vaccine hesitancy among those that are unvaccinated. Specifically, according to a study conducted by the Kaiser Family Foundation, 31% of individuals surveyed reported they would be more inclined to receive the COVID-19 vaccine if one of the vaccines authorized under EUA received full FDA approval.[3] These data demonstrate the importance of educating those who remain unvaccinated on the differences between EUA and FDA approval.

3 | CLINICAL TRIAL DATA

BNT162b2, mRNA-1273, and Ad26.COV2.S, each has received EUA (and full approval for BNT162b2) in the United States based on the totality of the data reviewed by the FDA. Each vaccine was evaluated in double-blind, randomized, placebo-controlled clinical trials for safety and efficacy. These studies each enrolled tens of thousands of participants with similar baseline characteristics.[4–6] For BNT162b2 and mRNA-1273, the primary efficacy endpoint was vaccine efficacy calculated as $100 \times (1 - [\text{attack rate with the vaccine}]/[\text{attack rate with the placebo}])$.[4,5] In contrast, vaccine efficacy for Ad26.COV2.S COVID-19 vaccine was calculated by $[(1 - \text{ratio (vaccine/placebo) of cumulative incidence by time t}) \times 100\%]$.[6]

3.1 | BNT162b2 mRNA COVID-19 vaccine (Pfizer/BioNTech)

BNT162b2 was evaluated in a two-dose vaccine series administered intramuscularly 21 days apart. Data for 37,706 participants met a cutoff date of October 9, 2020 to have at least 2 months of available safety data after the second dose of vaccine.[4] The primary efficacy endpoints evaluated confirmed cases of COVID-19 (defined as positive nucleic acid amplification test [NAAT] for SARS-CoV-2 with COVID-19 symptoms, Table 1) within 7 days after the second dose and in participants with or without prior SARS-CoV-2. The primary safety endpoints were development of adverse events (local or systemic) and use of an antipyretic or pain medication within 7 days of each vaccine dose or placebo.

Although some protection was conferred against COVID-19 after the first dose of active vaccine, optimal protection occurred 7 days after the second dose. Overall, data obtained from this analysis demonstrated 95.0% (90.3–97.6) vaccine efficacy (95% CI) against symptomatic COVID-19 in individuals 16 years and older over a median of 2 months meaning receipt of this vaccine reduced symptomatic COVID-19 when compared to no vaccine at all. Additionally, vaccine efficacy was similar regardless of age, gender, race, ethnicity, or coexisting conditions. The calculated vaccine efficacy and associated confidence interval met the FDA-pre-specified criteria for vaccine efficacy.

Pain at injection site was common after the first dose, while systemic reactogenicity was more common after the second dose in both the younger and older vaccine recipients. Mild-moderate local reactions tended to subside within 1–2 days. Fatigue, headache, and fever were the most common systemic reactions reported after the second dose of the vaccine. Fever and chills were typically observed within the first 1–2 days after vaccination and resolved shortly after. Younger vaccine recipients were more likely to take an antipyretic or pain medication (28% after first dose; 45% after second dose) than older recipients (20% after first dose; 38% after second dose) when compared to the placebo group (10%–14% after either dose).

3.2 | mRNA-1273 COVID-19 vaccine (Moderna)

mRNA-1273 was evaluated in a two-dose vaccine series administered intramuscularly 28 days apart in 30,420 participants (15,210 in each group).[5] The primary efficacy endpoint was COVID-19 (defined as RT-PCR positive SARS-CoV-2 with COVID-19 symptoms, Table 1) at least 14 days after the second injection in participants who were SARS-CoV-2 seronegative at baseline. Similar to BNT162b2, a cutoff date of November 25, 2020 occurred in order to provide at least 2 months of safety data after the second dose.

In this study, COVID-19 was more common in the placebo group compared with the mRNA-1273 group (Table 1). The vaccine efficacy (95% CI) was 94.1% (89.3%–96.8%) 14 days after administration of the second dose indicating reduced symptomatic laboratory-confirmed COVID-19 when compared to no vaccine against COVID-19. These findings met the FDA-pre-specified criteria for vaccine efficacy. A key difference that was noted in this analysis was the development of 30 cases of severe COVID-19 with 1 death in the placebo group compared with no cases of severe COVID-19 in participants receiving vaccination.

Injection-site reactions were generally mild and lasted 2.6 and 3.2 days after the first and second doses, respectively (Table 1). Delayed injection-site reactions (>8 days after injection) were rare (0.8% after first dose; 0.2% after second dose) and resolved within 5 days. Moderate-severe systemic reactogenicity (fatigue, myalgia, and headache) was commonly observed after the second dose of vaccine and began approximately 15 h after administration of the second dose. Like BNT162b2, younger participants categorized between the ages of 18 to <65 years were more likely to experience local and systemic reactogenicity.

3.3 | Ad26.COV2.S COVID-19 vaccine (Johnson and Johnson/Janssen)

The third vaccine to be granted EUA in the United States is a single-dose recombinant adenovirus type 26 vector.[6] In the pivotal study of Ad26.COV2.S, 19,630 participants received the vaccine and 19,691 received placebo. Primary endpoints in this analysis included vaccine efficacy against moderate to severe-critical COVID-19 at least 14 and 28 days after administration. Consistent with previous studies, to have enough safety data accrual, a data cutoff was instituted (January 22, 2021).

One hundred and sixteen cases of moderate to severe-critical COVID-19 occurred at least 14 days after vaccine administration compared with 348 in the placebo group. These data indicated that Ad26.COV2.S had a vaccine efficacy (95% CI) of 66.9% (59.0%–73.4%) against moderate to severe or critical COVID-19 compared with no vaccine against COVID-19. This point estimate and confidence interval met the FDA-pre-specified criteria for vaccine efficacy. Similar vaccine efficacy was seen 28 days after administration (Table 1). Differences between the vaccine and placebo groups in the development of COVID-19 became apparent 14 days after administration. The greatest protection the vaccine offered was against severe-critical COVID-19. Vaccine efficacy was reported to be 76.7% at least 14 days after administration and 85.4% at least 28 days post-administration.

Participants who received Ad26.COV2.S reported more local and systemic adverse events within 7 days of administration than those receiving the placebo (Table 1). Most local and systemic reactions appeared 1–2 days after administration and subsided in 1–2 days. Like the findings in the other vaccine trials, younger recipients experienced adverse events more frequently. Injection-site reactions occurred in almost half of the participants. Headache (39%), fatigue (38%), nausea (14%), and myalgia (33%) were the most common systemic reactions associated with the vaccine. Interestingly, venous thromboembolic events (VTE), seizures, and tinnitus were numerically higher in the vaccine group (VTE [11], seizure [4], and tinnitus [6]) compared with the placebo group (VTE [3], seizure [1], and tinnitus [0]). Three deaths occurred in the vaccine group, where none were COVID-related, compared with 16 in the placebo group, where 5 were COVID-related. Based on these findings, authors of this study concluded that a single dose of Ad26.COV2.S provided protection against asymptomatic SARS-CoV-2, as well as moderate to severe-critical COVID-19.[6]

In summary, three vaccines, BNT162b2, mRNA-1273, and Ad26.COV2.S, met the FDA pre-specified criteria for vaccine efficacy. Although there are some numerical differences between these vaccines, direct comparison between trials may not be possible due to differences in study design, SARS-CoV-2 strains, prevalence, and transmission dynamics. These items have been thoroughly reviewed elsewhere.[7] The remainder of this review examines these and additional factors to consider when interpreting COVID-19 vaccine studies conducted outside of randomized controlled trials.

4 | REAL-WORLD EFFECTIVENESS AND SAFETY OF COVID-19 VACCINES

Real-world data should also be considered to determine effectiveness of these vaccines outside of the highly controlled clinical trial environment. Several studies have examined how vaccination has affected documented SARS-CoV-2 infection, symptomatic SARS-CoV-2 infection (COVID-19), and asymptomatic SARS-CoV-2 infection (Table 2).[8-13] A nationwide study of BNT162b2 demonstrated that effectiveness mirrored the efficacy observed in the clinical trials for preventing documented SARS-CoV-2 infection and COVID-19.[8] BNT162b2 and mRNA-1273 also demonstrated effectiveness in high-risk individuals. In studies of healthcare workers, the proportion of those who became infected decreased with partial and complete vaccination status,[9] and SARS-CoV-2 incidence was 0.17% among vaccinated persons.[10] Collectively, these data suggest that in a real-world setting, these vaccines are highly efficacious at preventing SARS-CoV-2 infection.

Another important consideration is the effect of vaccination on asymptomatic SARS-CoV-2 infection. Asymptomatic spread of SARS-CoV-2 may be a large contributor to the propagation of COVID-19 cases.[14] Several observational studies have assessed the impact of vaccination on asymptomatic infection (Table 2). A retrospective cohort study of asymptomatic individuals screened during preprocedural testing found that vaccination decreased relative risk of SARS-CoV-2 any time after the second dose.[11] Another study found that vaccination decreased the incidence rate ratios for SARS-CoV-2 infection, asymptomatic SARS-CoV-2, and COVID-19 (or any SARS-CoV-2 after known exposure) in asymptomatic hospital workers.[13] In a different multistate, prospective cohort study of essential and frontline workers vaccine efficacy (95% CI) was estimated to be 91% (73%–97%) for reducing combined COVID-19 and asymptomatic SARS-CoV-2.[12] Together, the results of these studies indicate that BNT162b2 and mRNA-1273 are likely effective at reducing asymptomatic SARS-CoV-2, a major contributor of COVID-19 spread. Of note, while not a real-world study, Ad26.COV2.S was found to prevent asymptomatic infection in clinical trials.[6] It is also important to note that these studies were conducted prior to any meaningful effect of waning immunity or variants (see General Considerations for Immunity Post-Vaccination and Variants).

There are several important caveats to interpreting these data. In contrast to randomized controlled trials, these observational studies have many sources of heterogeneity. The first factor that clinicians should consider is the lack of uniform study design.[7] These subtle variations can lead to misleading comparisons of vaccine products. For example, case-control studies that match COVID-19 cases with controls that have COVID-19 symptoms but negative SARS-CoV-2 tests (test-negative design) may be susceptible to misclassification bias based on the SARS-CoV-2 test used.[15] Another consideration is measurement of vaccine effectiveness. Some of these studies quantify vaccine effectiveness as a function of 1—relative risk (RR) and others use hazard ratio (HR). While the RR and HR are both measures of association, they are not synonymous. Relative risks can differ

TABLE 2 Real-world effectiveness of COVID-19 vaccines

Vaccine	Population	Study design	Key endpoints	Key findings
BNT162b2[8]	Nationwide cohort (n = 596,618)	Matched cohort within integrated healthcare organization, unstructured testing	Vaccine Effectiveness (95% CI) for documented infection (VE-DI), symptomatic infection (VE-SI), and hospitalization (VE-H)[a]	VE-DI: 92% (88%–95%) VE-SI: 94% (87%–98%) VE-H: 92% (75%–100%)
BNT162b2 or mRNA-1273[9]	Healthcare workers (n = 23,234)	Cohort, unstructured testing	SARS-CoV-2 incidence in unvaccinated (UV), partially vaccinated (PV), and fully vaccinated (FV)[b]	UV: 2.61% PV:1.82% FV: 0.05% $p < 0.01$ for all pairwise comparisons
BNT162b2 or mRNA-1273[10]	Healthcare workers (n = 4167)	Cohort, weekly mandatory testing	SARS-CoV-2 incidence 15 or more days after second dose of either vaccine	0.17%
BNT162b2 or mRNA-1273[11]	Patients undergoing preprocedural tests (n = 48,333)	Cohort, mandatory testing	Relative risk[c] (95% CI) of SARS-CoV-2 in vaccinated vs. unvaccinated any time after second dose	0.20 (0.09–0.44)
BNT162b2 or mRNA-1273[12]	Multistate, prospective cohort study of healthcare workers, first responders, and other essential and frontline workers (n = 3950)	Active surveillance with weekly self-collected a midturbinate nasal swab	Vaccine effectiveness[d] (95% CI) for combined COVID-19 and asymptomatic SARS-CoV-2 infection	91% (73%–97%)
BNT162b2[13]	Asymptomatic hospital workers (n = 5217)	Cohort, minimum of once weekly testing	Incidence rate ratio (95% CI) for any SARS-CoV-2 infection (AC), asymptomatic SARS-CoV-2 (AS), COVID-19 or known exposure cases (CK)[e]	AC: 0.21 (0.15–0.28) AS: 0.28 (0.18–0.42) CK: 0.16 (0.10–0.25)

[a]Vaccine effectiveness calculated as 1−risk ratio, using Kaplan-Meier Estimator, ≥7 days post second dose of BNT162b2.

[b]Partially vaccinated individuals received one dose of BNT162b2 vaccine <7 days before index date or the second dose of mRNA-1273 vaccine less than 14 days before index date. Fully vaccinated persons were those who received the second dose of BNT162b2 vaccine at least 7 days before index date or the second dose of mRNA-1273 at least 14 days before the index date.

[c]Mixed effects log-binomial regression adjusted for age, sex, race/ethnicity, patient residence relative to the hospital (local vs. non-local), healthcare system regions, and repeated screenings among patients.

[d]Unadjusted vaccine effectiveness calculated as 100% × (1 − hazard ratio). Adjusted vaccine effectiveness (95% CI) with study site as covariate: 90% (68%–97%).

[e]Confirmed cases per person-days of follow-up in vaccinated compared with unvaccinated groups using Kaplan-Meier estimator.

TABLE 3　Activity of COVID-19 vaccines against SARS-CoV-2 variants of concern

Variant	BNT162b2		mRNA-1273		Ad26.COV2.S	
	In vitro reduction in neutralization activity[a]	Range for point estimates of clinical effectiveness[b]	In vitro reduction in neutralization activity[c]	Range for point estimates of clinical effectiveness[d]	In vitro reduction in neutralization activity[e]	Range for point estimates of clinical effectiveness[f]
Alpha (B.1.1.7)	0.8–1.3-fold[35,36]	85%–94%[41–45]	1.6-fold[36]	91%[45]	0.9-fold[40]	N/A
Beta (B.1.351)	10.3-fold[36]	75%–85%[41,45]	12.4-fold[36]	78%[45]	3.6-fold[40]	52%–64%[6]
Delta (B.1.617.2)	1.4-fold[37]	85%–88%[44,45]	2.1-fold[39]	70%[45]	1.6-fold[40]	N/A

Note: Fractional values indicate increased activity.

[a]Alpha: Muik et al. calculated 50% pseudovirus neutralization geometric mean titers (95% CI) ratios of variant to Wuhan strain. GMT (95% CI) 0.78 (95% CI: 0.68–0.89) for the younger group and 0.83 (95% CI: 0.65–1.1) for the older adults [0.80 (95% CI: 0.71–0.89) in aggregate. Reduction calculated as reciprocal of GMT ratio. Wang et al. Reciprocal serum ID_{50} in authentic virus assay ($p = 0.322$ vs. USA-WA1/2020). Beta: Wang et al. Reciprocal serum ID_{50} in authentic virus assay ($p = 0.002$ vs. USA-WA1/2020). Delta: Liu et al. calculated geometric mean titers ratios of USA-WA1/2020 (502) to B.1.617.2-spike (355). Reduction calculated as reciprocal of GMT ratio.

[b]Alpha and Beta: Abu-Raddad et al. calculated vaccine effectiveness as (1 – odds ratio for SARS-CoV-2 infection in vaccinated group) ×100% from test-negative case-control study ≥14 days after second dose. Hall et al calculated vaccine effectiveness as (1 – adjusted hazard ratio for SARS-CoV-2 infection in vaccinated group any time after first dose of vaccine). Adjusted hazard ratio calculated from piecewise exponential hazard mixed effects model (shared frailty-type model) and Poisson distribution. Sheik et al. calculated vaccine efficacy in preventing PCR-confirmed SARS-CoV-2 infection using test-negative analysis considering the whole population any time after one or two doses. Lopez Bernal et al. calculated vaccine effectiveness using test-negative case-control design and logistic regression to estimate odds of symptomatic, PCR-confirmed COVID-19 among vaccinated individuals as compared to unvaccinated individuals. Effectiveness was calculated ≥21 days after first dose or ≥14 days after second dose. Alpha, Beta, and Delta: Nasreen et al. calculated vaccine effectiveness as (1 – adjusted odds ratio for COVID-19 in vaccinated group) using test-negative design ≥14 days after dose 2 and reported effectiveness for Beta/Gamma in aggregate.

[c]Alpha: Wang et al. Reciprocal serum ID_{50} in authentic assay ($p = 0.064$ vs. USA-WA1/2020). Beta: Wang et al. Reciprocal serum ID_{50} in authentic assay ($p = 0.0005$ vs. USA-WA1/2020). Delta: Fold change over D614G.

[d]Alpha, Beta, and Delta: Vaccine effectiveness as (1 – adjusted odds ratio for asymptomatic SARS-CoV-2 and COVID-19 in vaccinated group) using test-negative design. Beta and Delta: Estimated 21 days after 1 dose only, due to no cases in fully vaccinated group.

[e]Alpha: $p = 0.118$. Beta: $p = 0.001$. Delta: $p = 0.007$. Alpha, Beta, and Delta: Fold change over B.1. of neutralization, IC_{50}.

[f]Beta: Data derived from South African cohort in clinical trial. Efficacy is for moderate to severe-critical COVID-19. Lower end of range is ≥14 days and upper range is ≥28 days post-vaccine.

from hazard ratios because the latter uses censorship to assess integrated probability of outcome over time, risks do not. Hence, risks may be more susceptible to bias from loss to follow-up as compared to hazards because risks do not inherently measure duration of subjects' time within the cohort. Another consideration is differences in testing schemes used to ascertain SARS-CoV-2 infections. Some of these studies used frequent, regular, mandatory testing, while others relied on self-selected testing. The frequent, regular, mandatory testing used in some studies is likely to capture more cases, so comparison between studies may be difficult. Endpoint definitions (asymptomatic SARS-CoV-2, symptomatic SARS-CoV-2 [COVID-19], severe COVID-19, hospitalization, and death) also differed between studies. Additionally, differences between which tests were used, which symptoms were assessed, and regional hospitalization patterns can also influence the interpretation of these data.

Other considerations include the study population being evaluated.[7] Populations with a high proportion of individuals in public-facing careers (eg, healthcare, food distribution) likely have a higher level of community exposure to SARS-CoV-2 than individuals who can shelter in place with minimal exposure. As a result, the incidence of SARS-CoV-2 estimates may be heterogeneous between those with public-facing exposure versus those without. Despite these limitations, it appears that the real-world effectiveness of these vaccines is like that which was observed in clinical trials.

Safety is another large concern among the public. In response, the US Centers for Disease Control and Prevention (CDC) established the V-safe adverse event monitoring system.[16] V-safe is a voluntary program where participants self-enroll to receive text messages that connect them to web-based surveys at various time points post-vaccination. While this is an improvement from Vaccine Adverse Event Reporting System (VAERS), a spontaneous and voluntary reporting system, V-safe is limited by the quality of information obtained. Two major issues include: (i) being a voluntary system means that full denominator data are unavailable to quantify incidence, and (ii) the program is smartphone/web-based and may disproportionately exclude certain populations who are technologically illiterate or from low socioeconomic backgrounds. Despite these issues, the occurrence of serious adverse events reported to V-safe has been low, not different than with other commercially available vaccines, and consistent with the clinical trials experience.[17] During the first week that vaccines were available, there were 21 cases of anaphylaxis reported to V-safe out of a 1.9 million doses administered, making the rate 11.1 cases per million doses. Most of these reactions occurred within the first 15 min of vaccine administration.[18] Nearly 75% of vaccine recipients experienced local injection-site reactions after both doses of mRNA vaccines. Systemic symptoms occurred in 69% of vaccine recipients with the most common being fatigue (53.9%), headache (46.7%), and myalgia (44.0%).[16]

It should be acknowledged that use of Ad26.COV2.S was briefly paused in the United States after cases of thrombosis-thrombocytopenia syndrome (TTS) were observed. TTS is characterized by acute blood clots and low platelets in patients with no recent exposure to heparin[19] If not recognized or treated in a timely manner,

TTS can be severely disabling and sometimes fatal.[19] At the time of the pause, the vaccine had already been administered in over 6.5 million individuals. It is unclear whether the occurrence of TTS among Ad26.COV2.S was greater than the expected rate in the general population. The median age of TTS cases was 40 and primarily occurred among women. Nonetheless, the FDA and CDC recommended resuming vaccine administration, and the exceptionally low risk of TTS was outweighed by the benefit of the vaccine. Additionally, the CDC recommend that women younger than 50 years old should especially be aware of their increased risk for TTS.[19]

Myocarditis after vaccination has also been observed. These concerns were initially highlighted in a case series of seven males ages 14–19 years old within 4 days after the second BNT162b2 dose.[20] Since its publication, data from the VAERS and Vaccine Safety Datalink (VSD) were investigated. Of the 1226 cases of myocarditis and pericarditis submitted to VAERS, 323 cases met CDC working definition for myocarditis following mRNA vaccination (BNT162b2, mRNA-1273).[21] Considering the number of doses administered to the public, VSD data demonstrate the myocarditis/pericarditis case rate after vaccination is extremely low at 4.4 cases (after dose 1) and 12.6 cases (after dose 2) per million mRNA (BNT161b2, mRNA-1273) doses given. While a single-dose strategy may appear attractive to further minimize the risk of myocarditis in adolescence, most confirmed myocarditis cases resolved promptly after medical care.[21] Given that the benefits of vaccination far outweigh any small safety signal after either dose 1 or dose 2, COVID-19 vaccination for patients 12 years of age and older continues to be recommended by the CDC and American Academy of Pediatrics (AAP).[19] Continued surveillance for both TTS and myocarditis is occurring. There are likely other adverse events to emerge, and clinicians should continually review CDC and FDA guidance for updates on special populations who should be aware of an increased risk of adverse events.

5 | GENERAL CONSIDERATIONS FOR IMMUNITY POST-VACCINATION

The data from both clinical trials and real-world settings are promising but additional clinical considerations remain important. First, it is essential to consider time to immunity, as that may have significant public health impact. For vaccines requiring two doses, immunity after one dose but prior to 14 days post-vaccination is approximately 50% (BNT162b2: 52.4%; mRNA-1273: 50.8%).[4,5] Upon completion of the vaccination schedules immunity increased to 95% and 94.1%, 7 days after BNT162b2 and 14 days after mRNA-1273, respectively. For individuals receiving the single-dose Ad26.COV2.S, most trial participants mounted a robust immune response 15 days after a single vaccination with significant protection by day 29 after receiving the vaccination.[6] These data support the CDC classification of individuals as "fully vaccinated" if they are 2 weeks after their second dose of BNT162b2 or mRNA-1273 or single dose of Ad26.COV2.S.[19]

Another important consideration is the duration of immunity post-vaccination. Although immunity is likely a multifaceted issue,

clinical data and study of antibodies may provide clues into the minimum duration of immunity after vaccination. Immunogenicity data are beginning to emerge 3- and 6-months after two-dose vaccination with mRNA-1273 and BNT162b2. These data suggest antibody activity persists for at least 6-months after the second vaccine across all age groups. Results from the BNT162b2 trial demonstrate persistent activity 6 months after vaccination against COVID-19 infection with an efficacy (95% CI) of 91.3% (89.0%–93.2%).[22] Antibodies after mRNA-1273 vaccination persisted 6 months after second vaccination with point estimates (95% CI) for geometric mean endpoint titers (GMTs) of 92,451 (57,148–149,562) in participants 18–55 years of age, 62,424 (36,765–105,990) in those 56–70 years of age, and 49,373 (25,171–96,849) in those 71 years of age or older.[23] Binding antibody half-life (95% CI) for mRNA-1273 was estimated to be 52 days (46–58) assuming a steady decay rate over time, and 109 days (92–136) assuming decay rate decreases over time.[23] Defined correlates of protection for SARS-CoV-2 infection have not been identified. Although the minimum antibody titer for human immunity to SARS-CoV-2 infection is currently unknown, data from animal models suggest pseudovirus-neutralizing antibody titers of approximately 50 could be associated with protection.[24] Additional data from a matched case-control study in healthcare workers who received BNT162b2 suggest breakthrough infections may be correlated with neutralizing antibody titers during the peri-infection period; however, specific protective titers were not defined.[25] Ongoing studies will hopefully further define this threshold and correlation with protection. Delineating this threshold will be important since future vaccination campaigns may use boosters to maintain antibodies above the immunity threshold. Nonetheless, these data are reassuring that BNT162b2 and mRNA-1273 provide durable long-term protection for at least 6-months against SARS-CoV-2. No long-term data were available on Ad26.COV2.S at the time of preparing this review. Given this evidence, the CDC and FDA advise against the use of SARS-CoV-2 antibody testing in vaccinated persons or to assess the need for vaccination in unvaccinated persons, as these tests are not validated to evaluate immunity or protection from COVID-19 infection.[26,27]

The robust immune response with vaccination is starkly contrasted with the variable response with natural SARS-CoV-2 infection. One longitudinal study sought to investigate the peak levels and dynamics of neutralizing antibody waning and IgG maturation over time after natural SARS-CoV-2 infection.[28] The authors discovered neutralizing antibodies behaved very differently among the 164 participants in this study. There were individuals who failed to develop neutralizing antibodies (12%), individuals with antibodies 20 days after symptom onset but seroreverted in less than 180 days (27%), individuals who remained antibody-positive at 180 days post-symptom onset (28%), individuals with persistent and minimal antibody decay (32%), as well as a small group who showed an unexpected increase in neutralizing antibodies 90–180 days after symptom onset (2%). The authors concluded that neutralizing antibody duration varies considerably among individuals after natural infection. Hence, relying on natural SARS-CoV-2 infection to produce immunity is not a reliable

substitute for vaccination. Providers must emphasize vaccination is the only means to provide a durable and reliable immune response as opposed to natural SARS-CoV-2 infection.

6 | ONE DOSE VS. TWO DOSE

At the time of publication, two vaccine administration strategies have evolved for vaccines requiring two doses: the standard method and the delayed second dose method (DSDM). The standard method consists of following the recommended intervals outlined by clinical trials. DSDM allows for second doses at a longer interval than was evaluated in clinical trials. The United Kingdom (UK) was the first country to implement the DSDM with BNT162b2.[29] Since then, other countries around the world adopted DSDM due to vaccine availability concerns.[30]

The theoretical basis of the DSDM with BNT162b2 stems from extrapolation of clinical trial data from 15 to 21 days post one dose. In this window, BNT162b2 had a vaccine efficacy (95% CI) of 89% (52%–97%).[4] When considering these estimates, there is mathematical rationale for vaccinating more people with one dose as compared to less people with two doses. However, risks associated with DSDM include suboptimal individual protection and increased genetic pressure for variants.

Modeling studies have provided some insight into the DSDM. An agent-based model suggested delaying the second dose of BNT162b2 was advantageous if immunity remained stable after one dose.[30] Another simulation revealed that the impact of DSDM on mortality was lessened if vaccination rate was high but vaccine efficacy was low.[31] However, sequential combination of standard dosing in those >65 years followed by DSDM in those remaining may result in decreased societal mortality when vaccine efficacy is high. These data are limited by the fact that these simulations use estimates of vaccine effectiveness following one dose, do not consider the potential for lower efficacy (<70%) and do not uniformly account for immune decay over time.

Knowing which patients have the lowest risk of waning immunity following the first dose would allow for a risk-stratified implementation of DSDM. One potential low-risk category would be patients who have been immunologically primed with a previous SARS-CoV-2 infection.[28] One dose may be comparable with a full vaccination series for these individuals.[32,33] In one study, a single dose of BNT162b2 or mRNA-1273 produced higher median reciprocal 99% inhibitory dose virus neutralization titers in those with previous SARS-CoV-2 infection (40,960, 40,960, and 80 for those with previous asymptomatic SARS-CoV-2, previous COVID-19, and antibody negative, respectively; $p < 0.001$).[32] Another study found that the 95% confidence interval for interval of the percentage of binding that was blocked by antibodies was higher in healthcare workers with a history of SARS-CoV-2 within 60 days (96.0%–97.0%) compared to those without infection (49.6%–66.2%) after one dose.[33] These data suggest that those who have been previously infected with SARS-CoV-2 may be ideal candidates for DSDM, especially within 60 days of infection.[33]

TABLE 4 Considerations for use of COVID-19 vaccines in individuals who are pregnant and lactating

Study design and population	Key findings
Sequelae of COVID-19 in pregnancy	

A living systematic review and meta-analysis of 73 studies (n = 67,721)[46]	• Odds ratios for outcomes (95% CI) compared with nonpregnant women of reproductive age
	  o Intensive care unit admission: 2.13 (1.53–2.95)
	  o Invasive ventilation: 2.59 (2.28–2.94)
	  o Extra corporeal membrane oxygenation: 2.02 (1.22–3.34)
	• Odds ratios for outcomes (95% CI) compared with pregnant women without COVID-19:
	  o All-cause mortality: 2.85 (1.08–7.51)
	  o Admission to the intensive care unit 18.58 (7.53–45.82)

Multinational cohort study of women in 18 countries (n = 2130)[47]	• Relative risks for outcomes (95% CI) compared with pregnant women without COVID-19
	  o Severe infections: 3.38 (1.63–7.01)
	  o Intensive care unit admission: 5.04 (3.13–8.10)
	  o Maternal mortality: 22.3 (2.88–172)

Maternal transfer of SARS-CoV-2 antibodies in cord blood	
Cohort, prior SARS-CoV-2 infection (n = 83)[48]	SARS-CoV-2 IgG detected in cord blood of 72/83 (87%) neonatal-mother pairs
Cohort, prior SARS-CoV-2 infection (n = 31)[49]	SARS-CoV-2 IgG detected in cord blood of 29/31 (94%) neonatal-mother pairs
Cohort, vaccinated with BNT162b2 or mRNA-1273 (n = 10)[50]	SARS-CoV-2 IgG detected in cord blood of 10/10 (100%) neonatal-mother pairs and in breastmilk
Safety and immunogenicity of COVID-19 vaccines	

Safety cohort from v-safe surveillance system, v-safe pregnancy registry, and Vaccine Adverse Event Reporting System (VAERS) (n = 35,691)[51]	• Similar reactogenicity profile to what is observed in nonpregnant persons.
	• Completed pregnancies
	  o Live birth occurred: 712/827 (86.1%)
	  o Spontaneous abortion: 104/827 (12.6%)
	  o Stillbirth: 1/827 (0.1%)

Comparative antibody response of BNT162b2 or mRNA-1273 in women who were pregnant, lactating, or neither (n = 103)[52]	• Similar immunogenicity among nonpregnant, pregnant, and lactating individuals • Median receptor binding domain-IgG antibody titer: nonpregnant (37,839), pregnant (27,601), lactating (23,497) • Median pseudovirus neutralization titers: nonpregnant (901), pregnant (910), lactating (783)
Comparative antibody response of BNT162b2 or mRNA-1273 in women who were pregnant, lactating, or nonpregnant (n = 131)[50]	• Vaccine-induced antibody titers similar between groups • Median (IQR) titers: pregnant (5.59 [4.68–5.89]), lactating (5.74 [5.06–6.22]), and nonpregnant (5.62 [4.77–5.98]), p = 0.24.

The DSDM method, despite original controversy, has been demonstrated in modeling to potentially provide benefit under certain conditions. Coupling the modeling predictions with data on vaccine-induced responses in varying patient populations will allow for more appropriate vaccine administration planning. For a country with high vaccination rates, the DSDM may not provide benefits. However, in countries with lower vaccination rates, during infection surges, and for specific populations, the DSDM or a risk-stratified variation of this may be appropriate.

7 | VARIANTS

Variants of concern (VOC) are SARS-CoV-2 with altered genetic sequences that may increase transmissibility, morbidity, and mortality associated with infection. There are numerous variants of concern identified at different points within the pandemic including but not limited to Alpha (previously B.1.1.7; emerged in the UK; Feb 2020), Beta (previously B.1.351, emerged in South Africa [SA] Feb 2020), Gamma (previously P.1., emerged in Brazil; Apr 2020), and Delta (previously B.1.617.2, emerged in India; Sep 2020).[34] In addition to the impact on patient outcomes, clinicians may also be concerned that currently available vaccine therapies may be less effective as compared to the wild type (WT) and the previous predominant variant, D614G. Therefore, it would be important to determine whether the current armamentarium of vaccines is effective against these variant strains.

In vitro and real-world assessments of vaccine neutralization and effectiveness with BNT162b2, mRNA-1273, and Ad26.COV2.S against Alpha, Beta, and Delta variants are emerging. In vitro data indicate that sera from BNT162b2, mRNA-1273, and Ad26.COV2.S may be

TABLE 5 Pediatric COVID-19 vaccine clinical trials

Vaccine	Inclusion	Vaccine schedule	NCT number
BNT162b2	12–15 years	2 doses 21 days apart	NCT04368728
BNT162b2	≥6 months to <2 years ≥2 to <5 years ≥5 to <12 years	2 doses 21 days apart	NCT04816643
mRNA-1273	12–17 years	2 doses 28 days apart	NCT04649151
mRNA-1273	≥6 months to <12 years	2 doses 28 days apart	NCT04796896
Ad26.COV2.S	12–17 years	1 or 2 doses Various schedules	NCT04535453

minimally impacted by Alpha (Table 3).[35,36] In contrast, sera of all three vaccines have reduced antibody neutralization efficacy against Beta and Delta.[35–40] These data are intriguing in that they demonstrate the potential impact of variants on immunity but should be interpreted with caution as in vitro data do not always correspond to in vivo response. Investigators have posited that reduced titers are unlikely to translate to clinical relevance because the resultant titers were above the minimum pseudovirus-neutralizing antibody titer (1:50) that was associated with partial protection in animal models.[24,36] Additionally, the reduced binding affinity and neutralization must be taken in the context of the entire immune response and the clinical experience.

The vaccines may be clinically effective against variants. BNT162b2 was found to be effective at preventing COVID-19, hospitalization, and death due to the Alpha and Beta variants in Qatar where nearly all cases of SARS-CoV-2 were due to either of the two variants (Table 3).[41] The UK experience with BNT162b2 was similar when the Alpha variant was the dominant circulating variant.[42] Additional studies have corroborated these findings.[43,44] mRNA-1273 has been found to be clinically effective against COVID-19 and hospitalization due to Alpha and Beta variants in a population-wide Canadian study.[45] Ad26.COV2.S was found to be efficacious at preventing moderate to severe-critical COVID in the South African cohort (a population with >95% Beta variants) during clinical trials. With regards to Delta, BNT162b2 vaccination has been shown to be effective at preventing COVID-19 and related hospitalization due to Delta variants.[43,44] mRNA-1273 was also found to be effective at preventing COVID-19, hospitalization, and death due to the Delta variant.[45] It is important to note that for those vaccines requiring two doses, efficacy increased after the second dose. In addition, as noted above, variance between study design makes it difficult to directly compare these study findings.

Further clinical data are needed to fully elucidate the effectiveness of these vaccines in the setting of SARS-CoV-2 genetic variants. As data emerge, it will be important to consider post-vaccination T-cell and B-cell responses to the variants, in addition to neutralizing antibody response. The impact of the variants will also be dependent on the overall variant prevalence. The current data available regarding effectiveness of mRNA vaccines are promising for the Alpha, Beta, and Delta variants despite documented reduction in neutralizing antibodies in vitro. Although, the true effectiveness against variants is difficult to ascertain due to the dynamic prevalence of these variants and the limited sero-typing resources for most areas across the world continued genotypic surveillance will be important to determine needs of vaccination programs. Furthermore, if immunity wanes, the impact of the variants may be augmented. The CDC provides an excellent overview of VOC/interest and their implications on the population and vaccine neutralization in the United States.[34]

8 | PERSONS WHO ARE PREGNANT AND LACTATING

Since the emergency use authorizations of these vaccines, the CDC, American College of Obstetrics and Gynecology, and the Society for Maternal and Fetal Health, each has recommended these vaccines be made available to persons who are pregnant and lactating.[19] But the organizations emphasize that the decision to get vaccinated during pregnancy and lactation should be an individualized decision. Interestingly, because pregnant persons were excluded from initial clinical trials, initial recommendations were mostly based on risk-benefit analysis. Specifically, the benefits of preventing severe COVID-19 infection in pregnant persons and the potential for transfer of maternal antibodies to the fetus and/or newborn, were weighed against the risks of developmental and reproductive toxicity and other vaccine adverse effects. Since the initial recommendations, clinical data have emerged and clinical trials for pregnant individuals (NCT04754594) have begun.

Pregnant individuals who contract COVID-19 are at high risk for adverse health outcomes (Table 4). This population has a higher risk of admission to the intensive care unit,[46,47] severe infection,[47] and maternal mortality[46,47] as compared to pregnant women without COVID-19. Compared with nonpregnant women of reproductive age, pregnant and recently pregnant persons with COVID-19 have higher odds for admission to the intensive care unit, invasive ventilation and need for extra corporeal membrane oxygenation.[46] Given these findings, it is reasonable to conclude that the prevention of

COVID-19 with vaccination would reduce mortality and admission to the ICU for COVID-19 in persons who are pregnant.

Another potential benefit of vaccination in persons who are pregnant is maternal transfer of SARS-CoV-2 antibodies from mother to fetus. Assessment of cord blood from mother-neonatal pairs has consistently demonstrated the presence of SARS-CoV-2 IgG.[48–50] This finding was observed for antibodies after natural infection[48,49] and vaccination.[50] Mothers also may transfer SARS-CoV-2 antibodies via breastmilk.[50] Although these studies are small, they suggest that maternal transfer of antibodies to the fetus and neonate is a likely benefit of vaccination.

With regards to risks, the teratogenic effects of these vaccines were examined in animal models prior to clinical trials and real-world data are beginning to corroborate these findings. To date, BNT162b2, mRNA-1273, and Ad26.COV2.S have not been associated with developmental and reproductive toxicity (DART) in animal models.[19] Preliminary safety data demonstrate no obvious safety signal in pregnant patients receiving BNT162b2 or mRNA-1273.[51] Data from v-safe surveillance system, v-safe pregnancy registry, and Vaccine Adverse Event Reporting System (VAERS) were used to assess local and systemic reactions as well as pregnancy outcomes in pregnant patients receiving either vaccine from December 14, 2020 to February 28, 2021.[51] Pregnant persons 16–54 years old (N = 35,691) reported injection-site pain, fatigue, headache, and myalgia as the most frequent local and systemic reaction after vaccination and were reported more frequently after the second dose. This reactogenicity profile is like what is observed in nonpregnant persons. Among patients in the v-safe pregnancy registry who completed a pregnancy, outcomes appear similar to previously published incidences in pregnant populations examined prior to COVID-19 and do not allude to an obvious risk with maternal vaccination.[51] Additional data are forthcoming for pregnancies that are currently uncompleted.

It is also prudent to examine the immunogenicity of these vaccines in pregnant individuals. Data indicate that the immune response to BNT162b2 and mRNA-1273 in persons who are pregnant and lactating is similar to nonpregnant, non-lactating women.[50,52] At this time, data were unavailable on the immunogenicity of Ad26.COV2.S in pregnant individuals, but are forthcoming. These data suggest that there is a strong immune response to BNT162b2 and mRNA-1273 in pregnant individuals. However, the exclusion of pregnant persons from clinical trials highlights need for systematic reform in clinical trials.

9 | PEDIATRICS

In 2019, children and adolescents comprised 22.7% of the United States population.[53] Thus, vaccinating this age group would have a significant impact on reducing the burden of SARS-CoV-2 in the community. The consideration of vaccine efficacy and safety, as well as the implications of COVID-19 infection in this age group, is critical to moving the vaccination campaign forward.

While most pediatric SARS-CoV-2 infections are asymptomatic or mild, the implications of disease are not benign in this population. After infection, pediatric patients are susceptible to multisystem-inflammatory syndrome in children (MIS-C), a severe life-threatening hyperinflammatory syndrome requiring ICU admission in 80% of cases.[54] SARS-CoV-2 also disproportionately affects Hispanic and black children as rates of infection, hospitalization, and MIS-C are increased in these groups compared with white children.[54,55] As of July 29, 2021, 17,059 children have been hospitalized and 358 children have died as a result of COVID-19 infection in the United States.[56] While it may be compelling to vaccinate only high-risk children, there is limited evidence about which underlying medical conditions might increase the risk for severe illness in children. Among children <18 years old admitted to the hospital for COVID-19, only 42% had one or more underlying high-risk medical condition, with obesity being the most prevalent (37.8%).[57] Therefore, vaccinating children against COVID-19 remains critical.

There is also concern that COVID-19 may become a disease of the young as more adults are vaccinated. According to the American Academy of Pediatrics and Children's Hospital Association, the incidence of disease among pediatrics is increasing each week, with children making up as high as 24% of incident COVID-19 cases in May 2021.[58] Cumulative cases also continue to increase in pediatrics, with percent total cases in May 2021 at 14% compared with <5% in spring 2020.

COVID-19 vaccine clinical trials are either ongoing or nearing completion in pediatric populations. As of May 2021, BNT162b2 has received emergency use authorization in patients 12 years of age and older. Authorization was granted for patients 12–15 years old based on a phase 2/3 clinical trial, which demonstrated 100% efficacy in preventing COVID-19 infection (defined as symptomatic, laboratory-confirmed SARS-CoV-2) seven days after the second dose.[59] BNT162b2 was also well tolerated in adolescence receiving the study vaccine, with similar reactogenic effects observed in the 16–25 age group.[59] Additional clinical trials for BNT162b2, mRNA-1273, and Ad26.COV2.S are ongoing in various age groups from 6 months through 17 years (Table 5).

The Advisory Committee on Immunization Practices and American Academy of Pediatrics support co-administration of the COVID-19 vaccine with other routine childhood and adolescent vaccines.[19,60] This is particularly important as overall routine pediatrician vaccine orders from the Vaccine for Children Program are currently down by 11.7 million doses compared with 2019.[56] According to the CDC, providers and pharmacists are encouraged to administer the COVID-19 vaccine without regard to timing of other immunizations in all populations.[19]

10 | CONCLUSIONS

Three vaccines (BNT162b2, mRNA-1273, and Ad26.COV2.S) are currently authorized for emergency use in the United States. Each has demonstrated safety and efficacy in large, well-designed randomized controlled trials involving thousands of participants. Real-world data have corroborated findings from the clinical trials.

Emerging data indicate that immunity is conferred within 2 weeks of vaccination and may last at least 6 months. Data indicate that some vaccines may be effective against SARS-CoV-2 VOC. Finally, populations not included in the original studies may also benefit from vaccination. Combined, these data suggest that the vaccines will be critical in ending the COVID-19 pandemic.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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