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COVID-19 Vaccines

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KEYWORDS

• COVID-19 • Janssen (Ad.26.CoV2) • SARS-CoV-2 • Vaccine • mRNA vaccine • vaccine efficacy trials • post-marketing vaccine surveillance

KEY POINTS

- The degree of clinical protection against COVID-19 provided by vaccination remains an incredible triumph of modern science.
- Analysis of data generated from "real-world" vaccination cohorts have recapitulated the striking degree of efficacy of vaccination against clinical disease, especially severe disease, observed in randomized controlled trials.
- Although there may be subtle differences with respect to the duration of protection against mild illness conferred by various vaccine products, these differences pale in comparison to the difference between the unvaccinated and those with only immunity following natural infection.

INTRODUCTION

Within 1 year of the first identification of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a series of landmark clinical trials involving a variety of vaccine approaches unequivocally demonstrated that coronavirus disease 2019 (COVID-19) was a vaccine-preventable illness.[1–7] Since the initial demonstration of clinical efficacy in the fall of 2020, several products have achieved authorization or licensure and billions of persons have been vaccinated worldwide. All vaccine candidates to date have demonstrated a high degree of efficacy against hospitalization and severe disease. However, there has been wide variation in the reported efficacy against infection and mildly symptomatic disease, and questions remain whether there are significant differences in the durability of the clinical protection elicited by various vaccine platforms. This review is an attempt to briefly summarize a fast-moving field, with an emphasis on clinical efficacy established in both randomized trials and postmarketing surveillance. Important efforts to address concerns regarding vaccine equity, including the racial and ethnic disparities associated with vaccine access, are addressed elsewhere in Chapter 4.

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Overview of Vaccine Efficacy Trials: Rapid Design and Implementation

Approximately 6 months after the initial description of a respiratory virus syndrome associated with SARS-CoV-2 infection, efficacy trials were initiated in several countries. Within 10 months several products were clinically available, which have now been administered to billions of persons worldwide. The incredible pace of the development schedule has prompted questions from the public regarding whether safety or data quality were compromised in the pursuit of speed. For reference, the shortest development cycle under modern approval mechanisms was approximately 5 years for an Ebola vaccine, and a typical vaccine approval cycle takes 10 to 15 years[8]; the old paradigm for vaccine development timelines has been shattered.

The time savings during the development of COVID-19 vaccines was achieved via unparalleled degrees of public financial support and a higher tolerance for at-risk investment into the technology and process, when compared with previous vaccine development cycles. Some of the key efficiency gains were achieved by immediately initiating efficacy trials after establishing that vaccines were safe and immunogenic rather than waiting for information regarding the durability of the immune response (as would be typical). To further increase the pace of the COVID-19 vaccine trials, a large population was enrolled with a "time-to-event" trial design, whereby prespecified efficacy analysis was based on a specific number of observed infections rather than a predefined observation period. From the implementation side, large amounts of vaccines were manufactured before the establishment of clinical efficacy, meaning that there was substantial risk that resources devoted to manufacturing a vaccine with unknown efficacy could have been wasted if the vaccine failed to provide clinical protection. By manufacturing a large amount of candidate vaccines before demonstrating these vaccines are effective, national health authorities were able to rapidly roll out massive vaccination campaigns immediately after the vaccines were shown to be clinically efficacious. It is important to note that whereas private industry developed and sponsored many of the trials, public dollars supported the trials, substantially decreasing the risk to a particular company from both the clinical trial and manufacturing perspectives.

Currently Approved Vaccines: Overview

The current regulatory landscape is rapidly evolving, but 3 vaccines have achieved emergency use authorization (EUA) in the United States as of 2021: BNT162b2 from Pfizer-BioNTech, mRNA-1273 from Moderna, and the Ad26.COV2.S product from Janssen Pharmaceuticals. The Pfizer (BNT162b2) vaccine has since achieved biologic license application approval from the US Food and Drug Administration (FDA). All 3 have seen widespread implementation, with mRNA vaccines comprising most vaccinations in the United States. Both the Pfizer (BNT162b2) and Moderna (mRNA-1273) vaccines comprise 2 doses, whereas the Janssen vaccine (Ad26.COV2.S) is approved as a one-dose regimen. Advanced candidate vaccines that have undergone (or are undergoing) phase 3 trials to support licensure in the United States include products from Sanofi, Novavax, and AstraZeneca (AZ); these products are undergoing FDA regulatory review, but the approval timeline for these products has not been established as of early 2022. Other vaccines have achieved international licensure but are not, to date, conducting trials to support licensure in the United States.

All vaccines to date target the spike protein of the SARS-CoV-2 virus using a variety of platforms to deliver the spike antigen, including mRNA encapsulated in lipid

nanoparticles (LNP) (Pfizer and Moderna), replication-incompetent viruses (AZ/University of Oxford, Janssen, Gameleya), or recombinant proteins (Novavax). Except for the AZ product, all other vaccines in advanced stages in the United States use a modified spike protein designed to be more stable in the prefusion state; the AZ product uses a native sequence. There are more than 50 candidate vaccines in various stages of clinical testing using a variety of approaches; the specific details of these products are beyond the scope of this review.

All phase 3 efficacy trials have been randomized, placebo-controlled trials with laboratory confirmed SARS-CoV-2 infection in combination with symptomatic COVID-19 disease considered the primary end points. The prespecified statistical analysis plan of each trial to date conducted in the United States included a minimum number of clinical end points that triggered an interim analysis (typically around 100–150 cases). In general, the protocols were designed assuming a much lower rate of community transmission than was observed (an assumption of ~1% of placebo recipients per year becoming infected vs an observed rate of ~5%–10% per year); the high rate of community transmission was an underappreciated contributor to the rapid pace of determining that a given vaccine was effective. All the landmark trials reported in the following discussion were conducted before the emergence of the Delta or Omicron variants. Sanofi is currently testing their product and likely will have data from the period coinciding with the emergence of the Delta and Omicron variants.

Safety Data from Phase 3 Efficacy Trials

Although it is somewhat counterintuitive given the rapid pace of vaccine approval, the COVID-19 vaccine trials generated substantially more short-term safety data than would be available during a typical vaccine approval process. For example, each of the efficacy trials intended for licensure in the United States have enrolled (or plan to enroll) approximately 30,000 participants, with between 15,000 and 20,000 administered study product. For comparison, the RESOLVE trial, which was intended to support licensure of a vaccine against lower respiratory tract infection caused by respiratory syncytial virus in older adults only enrolled 11,856 participants with 1:1 randomization, meaning only 5921 participants were administered the study product (https://clinicaltrials.gov/ct2/show/NCT02608502).

Despite the large number of trial participants leading to abundant safety data, important safety signals for these vaccines were only determined with postmarketing surveillance after widespread implementation (see later discussion).

The generally consistent vaccination strategy between products (with 5 of the 6 major vaccine platforms produced in the United States including the same inserts of the spike protein of SARS-CoV-2) offers an unprecedented capacity for comparing the safety profile and performance across various platforms. An important technical note is the conceptual differentiation in safety outcomes between reactogenicity (eg, transient symptoms such as malaise or arm pain) and serious adverse events attributable to the vaccine (eg, Guillain-Barré syndrome [GBS]). The former are quite common with all vaccines, whereas the latter are extremely rare. The Centers for Disease Control and Prevention (CDC) is actively monitoring vaccines implemented using an EUA with several postmarketing surveillance programs.

All vaccines in which trial data have been reported were found to be safe and effective against both mild and severe disease (the Sanofi trial has not reported outcomes as of this writing). All vaccines used the same insert, a SARS-CoV-2 full-length spike, modified with 2 prolines that lock the protein into a form similar to the form the protein has before fusion with the target host cell. Both the Moderna (mRNA 1273) and the

Pfizer (BNT162b2) vaccines require an established cold chain capable of storage at −20°C to 70°C depending on the product, whereas the Janssen adenovirus vector vaccine (Ad26.COV2.S) can be stored for months in a refrigerator (4°C).

Although it is now incontrovertible that clinical COVID-19 can be prevented by vaccination, there are major outstanding questions about how SARS-CoV-2 will evolve in response to immune pressure from both natural immunity and immunity induced by the current generation of SARS-CoV-2 vaccines. In addition, as new variants, such as Delta and Omicron spread, the efficacy of current vaccines against asymptomatic and mild infection, and therefore also in interrupting transmission, is less clear, even while vaccines designed against the ancestral strain retain strong effectiveness against severe disease and death.

Moderna (mRNA-1273)

The Moderna vaccine (mRNA-1273) product is a 100 μg dose of the SARS-CoV-2 spike protein encoded by mRNA and LNP, developed by Moderna and the Vaccine Research Center within the National Institutes of Health. The regimen tested was a 2-dose regimen, administered with a 4-week interval between doses.

Phase 3 clinical trial ("COVE" trial) (**Table 1**) gave the following results:

- Results from a phase 3 randomized, observer-blinded, placebo-controlled trial of the Moderna SARS-CoV-2 vaccine candidate (mRNA-1273) indicated that the vaccine showed 94.1% efficacy at preventing COVID-19 (ancestral and alpha variants), including severe disease. A total of 30,420 volunteers were enrolled (15,210 placebo, 15,210 vaccine).
- Efficacy was similar across key secondary analyses, including in participants who had evidence of SARS-CoV-2 infection at baseline and analyses in participants aged 65 years or older.
- Serious adverse events were rare, and the incidence was similar to placebo.
- Reactogenicity after 1 dose was generally mild to moderate with pain reported as the most common injection site symptom. For systemic reactogenicity symptoms, 54.9% of participants reported solicited adverse events after the first dose (compared with 42.2% of placebo), and this increased to 79.4% with the second dose (compared with 36.5% with placebo). To place this rate in context with other vaccines, the rate of systemic reactogenicity after the first dose is less than that observed for the recombinant adjuvanted zoster vaccine and after the second mRNA-1273 dose is similar.[9] The Shingrix vaccine is a licensed vaccine generally considered to have a "moderate" degree of reactogenicity.

PFIZER (BNT162b2)

The Pfizer product (BNT162b2) is a 30 μg dose of the SARS-CoV-2 spike protein encoded by mRNA and encapsulated with LNP, developed by BioNTech and Pfizer.

Table 1
Phase 3 clinical trial ("COVE" trial)

	Cases that Meet Primary End Point	Severe Cases
Vaccine	11	0
Placebo	185	30

Data from Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2021;384(5):403–16.

The regimen tested was a 2-dose regimen, administered with a 3-week interval between doses.

Results of the phase 3 double-blind, randomized, placebo-controlled trial for the BioNTech and Pfizer mRNA vaccine (BNT162b2) (n = 21,720 in vaccine group, and 21,728 in placebo group) showed a vaccine efficacy of 95% (95% confidence interval [CI], 90.3–97.6) against ancestral strain and Alpha variant, with 8 cases of COVID-19 (1 severe case) in the vaccine group and 162 cases (9 severe cases) in the placebo group (**Table 2**).

Efficacy was similar across subgroups defined by age, sex, race, ethnicity, body mass index, and presence of coexisting conditions.

Mild to moderate reactogenicity was commonly observed and more frequent with the second dose. Severe fatigue was observed in approximately 4% of Pfizer (BNT162b2) vaccine recipients.

Few participants in either group had severe or serious adverse events, and the 6 deaths (2 in vaccine group, 4 in placebo group) were determined by investigators not to be related to the vaccine or placebo.

JANSSEN (Ad26.COV2.S)

The Janssen (pharmaceutical division of Johnson and Johnson) vaccine product was tested as single-dose regimen in the ENSEMBLE trial (**Table 3**). The vaccine includes the same insert as the Pfizer (BNT162b2) and Moderna (mRNA-1273) products but uses a well-established replication-incompetent adenovirus (Ad26) as a delivery package. The trial was conducted internationally, with 44% of participants enrolled in the United States, 41% of participants enrolled in South America, and 15% in South Africa. Of note, unlike either the Moderna (mRNA-1273) or Pfizer (BNT162b2) trial, the timing of the ENSEMBLE trial coincided with the emergence of the beta variant (B1.351) in South Africa.[3] As the vaccine was administered as a 1-dose regimen, data regarding protection at both 14 and 28 days (more analogous to the mRNA trials) after administration are presented.

The level of protection against moderate to severe COVID-19 infection was 72% in the United States, 66% in Latin America, and 57% in South Africa 28 days postvaccination. Molecular sequencing of the breakthrough cases suggests a much higher presence of the beta variant in breakthrough cases, in line with the reported epidemiology of the pandemic in South Africa.

VACCINE SAFETY GATHERED FROM POSTMARKETING SURVEILLANCE STUDIES

Allergic Reactions

Anaphylaxis has been rarely observed following vaccination with the mRNA vaccines. In one postmarketing study, 21 cases of anaphylaxis were determined to be related to vaccination (a rate of 11.1 per million doses administered), including 17 in people with prior documented history of allergies/allergic reactions, 7 of whom had a prior history of anaphylaxis. The median interval from vaccine receipt to symptom onset was

Table 2
Pfizer-BioNtech (BNT162b2)

	Cases that Meet Primary End Point	Severe Cases
Vaccine	8	1
Placebo	162	9

Table 3
Janssen (Ad26.COV2.S) ENSEMBLE trial

	Cases that Meet Primary End Point at D14	Cases that Meet Primary End Point at Day 28	Severe Cases at Day 14	Severe Cases at Day 28
Vaccine	114	65	14	5
Placebo	365	193	60	34

13 minutes.[10] The incidence of acute allergic reactions in health care workers (HCW) who received mRNA COVID-10 vaccines from December 16, 2020, to February 12, 2021, was assessed in a prospective observational cohort study conducted in Boston, Massachusetts. Of the HCW who received an mRNA COVID-19 vaccine and completed a symptom survey, 98% had no symptoms of an allergic reaction (different from true anaphylaxis). Acute allergic reactions were slightly more frequent with the Moderna vaccine (mRNA-1273) (2.20%) compared with Pfizer (BNT162b2) (1.95%), and anaphylaxis occurred at a rate of 2.47 cases per 100,000 vaccinations (similar rates between the Moderna [mRNA-1273] and Pfizer [BNT162b2]). Anaphylaxis was confirmed in 16 HCW, of whom 63% (n = 10) reported prior allergic reaction and 31% (n = 5) reported prior anaphylaxis.[11,12]

Another study performed analysis of safety surveillance data from Vaccine Safety Datalink of 10,162,227 vaccine-eligible members of 8 participating US health plans from December 14, 2020, through June 26, 2021. A total of 11,845,128 doses of mRNA vaccines (57% Pfizer [BNT162b2]: 6,175,813 first doses and 5,669,315 second doses) were administered to 6.2 million individuals (mean age, 49 years; 54% female individuals). Incidence of confirmed anaphylaxis was 4.8 (95% CI, 3.2–6.9) per million doses of Pfizer (BNT162b2) and 5.1 (95% CI, 3.3–7.6) per million doses of Moderna (mRNA-1273).

The current hypothesis is that the reaction is to polyethylene glycol, a preservative used in the vaccines. Persons with a history of hypersensitivity to polyethylene glycol or anaphylaxis to the first dose of an mRNA series should be vaccinated with an alternate product, such as the Janssen (Ad26.COV2.S) vaccine. Similarly, rare persons are known to have severe allergies to polysorbate—present in the Janssen adenovirus vaccine—and these individuals should be vaccinated with an mRNA vaccine.

In addition, there are a wide range of rashes and other skin findings associated with mRNA vaccine administration. None of these are life threatening. One notable finding with the mRNA vaccine is a delayed, local reaction where substantial erythema/induration is observed at the injection site on or around day 8 postvaccine administration; these do not represent true allergy, and patients have safely received repeat vaccinations.

KEY POINTS [TEXT BOX]

- Allergic reactions occur a median of ~15 minutes after product administration
- No cross-reactivity between mRNA and adenoviral vectors, so even a person with documented allergy should be eligible for continuing the series or boosting with an alternative product.
- Delayed injection site reactions (onset on or after day 8) have been reported in ~0.5% to 1% of participants after the first dose; subsequent doses are well tolerated, and therefore delayed injection site reactions are not a contraindication to booster doses.

Myocarditis

Several studies have reported the rare diagnoses of myocarditis following the COVID-19 mRNA vaccines, typically in young men and adolescent boys. In one population-based cohort study of 2,292,924 individuals (median age 49 year old) who received at least 1 dose of COVID-19 mRNA vaccines, acute myocarditis was rare, at an incidence of 5.8 cases per 1 million individuals after the second dose (1 case per 172,414 fully vaccinated individuals).[13] Another study noted that during a 3-month period between February 1, 2021, and April 30, 2021, 7 patients with acute myocarditis were identified, of which 4 occurred within 5 days of COVID-19 vaccination. Three were younger men (age, 23–36 years), and 1 was a 70-year-old woman. All 4 had received the second dose of an mRNA vaccine (2 received Moderna [mRNA-1273], and 2 received Pfizer [BNT162b2]).[14] A retrospective case series of patients within the US Military Health System who experienced myocarditis after COVID-19 vaccination between January and April 2021 identified 23 men (median [range] age, 25 [20–51] years); during this time period more than 2.8 million doses of mRNA COVID-19 vaccine were administered.[15] Data from the largest health care organization in Israel to evaluate the safety of the Pfizer vaccine (BNT162b2) also noted an excess risk of myocarditis in the vaccinated. The control and vaccinated groups each included a mean of 884,828 persons, and vaccination was most strongly associated with an elevated risk of myocarditis (risk ratio, 3.24; 95% CI, 1.55–12.44).

SARS-CoV-2 infection itself is much more strongly associated with increased risk of myocarditis (risk ratio 18.28; 95% CI, 3.95–25.12) with an excess risk of myocarditis (1–5 events per 100,000 persons).[16] In another study of more than 2.5 million vaccinated persons (who were $\geq$16 years old) in this same large health care system, 54 cases met the criteria for myocarditis. Of those who received at least one dose of the Pfizer (BNT162b2) vaccine, the estimated incidence of myocarditis was 2.13 cases per 100,000 persons; the highest incidence was among male patients between the ages of 16 and 29 years (10.69 cases per 100,000 persons). Most cases of myocarditis were mild or moderate in severity.[17] Although the rare risk of myocarditis with mRNA vaccines has been reported, the known risk of morbidity, including cardiac injury and myocarditis, following COVID-19 infection should be taken into consideration.[15]

KEY POINTS

- Risk of myocarditis with COVID-19 infection is higher than with COVID-19 vaccination.
- Myocarditis risk is highest in the first week after a second dose of mRNA vaccine.
- The risk is highest in adolescent boys and young men

Vaccine-Induced Thrombosis and Thrombocytopenia

Cerebral venous sinus thrombosis (CVST) associated with severe thrombocytopenia and disseminated intravascular coagulation that resembles autoimmune heparin-induced thrombocytopenia has been reported in recipients of the Janssen (Ad26.COV2.S) vaccine and recipients of the AZ vaccine (AZD1222 (ChAdOx1-S nCCoV-19). By April 12, 2021, approximately 7 million Janssen (Ad26.COV2.S) vaccine doses were administered in the United States and 6 cases of CVST with thrombocytopenia were diagnosed among recipients, resulting in a temporary pause in vaccination on April 13, 2021. A case series of 12 US patients with CVST and

thrombocytopenia following use of the Janssen (Ad26.COV2.S) vaccine was reported to the Vaccine Adverse Event Reporting System (VAERS) from March 2 to April 21, 2021 (with follow-up reported through April 21, 2021). Patient ages ranged from 18 to less than 60 years; all were white women. The time from vaccination to symptom onset ranged from 6 to 15 days. Of the 12 patients with CVST, 7 also had intracerebral bleed; 8 had non-CVST thromboses.[18] On April 23, 2021, the CDC and the FDA recommended that the use of Janssen (Ad26.COV2.S) vaccines resume in the United States, noting that the potential benefits of the vaccine outweigh the potential and known risks.[19] The CDC and FDA also noted that women younger than 50 years should be made aware of alternative COVID-19 vaccine options for which this risk has not been seen and should be made aware of the rare, but increased, risk for CVST. For these reasons, the CDC generally recommends use of mRNA vaccines over the Janssen (Ad26.COV2.S) product in most situations.

KEY POINTS

- Even with extremely low risk of vaccine-induced thrombosis and thrombocytopenia due to adenovirus-vectored vaccines, women younger than 50 years should be made aware of mRNA vaccines if available.
- The CDC currently recommends mRNA vaccines over Janssen (Ad26.COV2.S) based on the differences in safety profile

Guillain-Barré Syndrome

The US FDA also identified a potential safety concern for GBS following Janssen (Ad26.COV2.S) vaccination.[20] Presumptive GBS reports were noted via VAERS between February and July 2021, and as of July 24, 2021, 130 reports of presumptive GBS were identified following Janssen (Ad26.COV2.S) vaccination (median age, 56 years; 111 persons [86.0%] were < 65 years; 77 men [59.7%]). Most reports (93.1%, n = 121) were serious, including 1 death. The estimated crude reporting rate was 1 case of GBS per 100,000 doses administered. The overall estimated observed to expected rate ratio was 4.18 (95% CI, 3.47–4.98) for the 42-day window following immunization, and in the worst-case scenario analysis for adults 18 years or older, corresponded to an estimated absolute rate increase of 6.36 per 100,000 person-years compared with a background rate of approximately 2 cases per 100,000 person-years. For both risk windows, the observed to expected rate ratio was elevated in all age groups except persons aged 18 through 29 years. These findings suggest a small but statistically significant safety concern for GBS following receipt of the Janssen (Ad26.COV2.S) vaccine.[20] Notably, this increase in risk is less than the increased risk of GBS observed following natural SARS-CoV-2 infection.[21]

KEY POINTS

- Risk of GBS is higher with natural SARS-CoV-2 infection than with vaccination with adenovirus-vectored vaccines.

POSTMARKETING STUDIES OF REAL-WORLD EFFICACY

mRNA Vaccines

Adults older than 50 years

High mRNA vaccine effectiveness among older adults has been reported. A common approach to establishing efficacy in a real-world setting is a "test-negative" design. In this approach, patients tested clinically for SARS-CoV-2 infection are compared with those who tested negative. These analyses are relatively easy to conduct, but one potential criticism is that the underlying indication for testing can change based on the population (eg, asymptomatic screening vs patients presenting with upper respiratory tract symptoms). A study of adults (>50 years old) with COVID-19-like illness who underwent SARS-CoV-2 molecular testing evaluated 41,552 hospital admissions and 21,522 visits to emergency department or urgent care clinics in multiple states from January 1 through June 22, 2021. The effectiveness of full mRNA vaccination (>14 days after the second dose) was 89% against laboratory-confirmed SARS-CoV-2 infection leading to hospitalization, 90% against infection leading to an intensive care unit admission, and 91% against infection leading to an emergency department or urgent care clinic visit (against ancestral or Alpha strains). The effectiveness of full vaccination with respect to a COVID-19-associated hospitalization or emergency department or urgent care clinic visit was similar with the Pfizer (BNT162b2) and Moderna (mRNA-1273) vaccines and ranged from 81% to 95% among adults aged 85 year or older, those with chronic medical conditions, and black or Hispanic adults.[22] Another study found that among adults aged 65 to 74 years, effectiveness of full vaccination for preventing hospitalization was 96% for Pfizer (BNT162b2) and 96% for Moderna (mRNA-1273) and among adults aged 75 years or older, effectiveness of full vaccination for preventing hospitalizations was 91% for Pfizer (BNT162b2) and 96% for Moderna (mRNA-1273).[23]

All adult populations

One early study was conducted during a nationwide mass vaccination in Israel's largest health care organization of persons newly vaccinated with Pfizer (BNT162b2) between December 20, 2020, and February 1, 2021. Each study group (vaccinated and unvaccinated controls) included 596,618 persons. Estimated vaccine effectiveness at days 14 through 20 after the first dose and at 7 days or more after the second dose was as follows: for documented infection, 46% and 92%; for symptomatic COVID-19, 57% and 94%; for hospitalization, 74% and 87%; and for severe disease, 62% and 92%, respectively (ancestral strain and Alpha variant). Estimated effectiveness in preventing death from COVID-19 was 72% for days 14 through 20 after the first dose. The effectiveness in specific subgroups evaluated for documented infection and symptomatic COVID-19 was consistent across age groups, with potentially slightly lower effectiveness in persons with multiple coexisting conditions.[24] Another early study during December 14, 2020, to April 10, 2021, with data from the HEROES-RECOVER Cohorts, a network of prospective cohorts among frontline workers, found that both the Pfizer (BNT162b2) and Moderna (mRNA-1273) mRNA COVID-19 vaccines were approximately 90% effective in preventing symptomatic and asymptomatic COVID-19 infections.[25]

US studies noted high mRNA vaccine effectiveness as well. The effectiveness of mRNA vaccines against COVID-19-associated hospitalization among 1175 US veterans aged 18 years or older at 5 Veterans Affairs Medical Centers (VAMCs) during February 1 to August 6, 2021 (when the B.1.617.2 [Delta] variant was dominant) was measured. The overall adjusted vaccine effectiveness against COVID-19-associated hospitalization was 86.8% and was similar before (February 1 to June 30) and during

(July 1 to August 6) SARS-CoV-2 Delta variant predominance (84.1% vs 89.3%, respectively). Vaccine effectiveness was 79.8% among adults aged 65 years or older and 95.1% among veterans aged 18 to 64 years.[26] A test-negative, case-control analysis of 3689 US adults aged 18 years or older hospitalized at 21 US hospitals across 18 states during March 11 to August 15, 2021, was performed, and among adults without immunocompromising conditions, vaccine effectiveness against COVID-19 hospitalization was 93% for the Moderna (mRNA-1273) vaccine and 88% for the Pfizer (BNT162b2) vaccine.[27]

Studies of mRNA vaccine effectiveness that extended over longer periods and further into the Delta variant surge continued to note high vaccine effectiveness, although declines in effectiveness from earlier studies were reported. A matched test-negative, case-control study designed to estimate vaccine effectiveness against any SARS-CoV-2 infection and against any severe, critical, or fatal case of COVID-19, from January 1 to September 5, 2021, was performed, and the estimated Pfizer (BNT162b2) vaccine effectiveness against any SARS-CoV-2 infection reached its peak at 77.5% in the first month after the second dose. Thereafter, the effectiveness gradually declined, with the decline accelerating (after the fourth month) to approximately 20% in months 5 through 7 after the second dose. Variant-specific effectiveness waned in the same pattern. This contrasted with the pattern seen for severe disease where following vaccination, effectiveness against any severe, critical, or fatal case of COVID-19 was 66.1% by the third week after the first dose and reached 96% or higher in the first 2 months after the second dose; effectiveness persisted at approximately this level for 6 months.[28] Another large US health care system study assessed Pfizer (BNT162b2) vaccine effectiveness against SARS-CoV-2 infections and COVID-19-related hospital admissions among more than 3.4 million individuals between December 14, 2020, and August 8, 2021. For the fully vaccinated, effectiveness against SARS-CoV-2 infections was 73%, and against COVID-19-related hospital admissions it was 90%. Effectiveness against infections declined from 88% during the first month after full vaccination to 47% after 5 months. For those who received 2 doses, effectiveness against SARS-CoV-2 infections was 73%, and against COVID-19-related hospital admissions it was 90%. Effectiveness against infections declined from 88% during the first month after full vaccination to 47% after 5 months.[29]

Janssen (Ad26.COV2.S) Vaccine

Adults older than 50 years

A study of adults (>50 years of age) with COVID-19-like illness who underwent molecular testing for SARS-CoV-2) assessed 41,552 hospital admissions and 21,522 visits to emergency department or urgent care clinics between January 1 and June 22, 2021, in multiple states. The effectiveness of the Janssen vaccine (Ad26.COV2.S) was 68% against laboratory-confirmed SARS-CoV-2 infection leading to an emergency department or urgent care clinic visit.[22] Among adults aged 65 to 74 years, effectiveness of full vaccination for preventing hospitalization was 84%, and among adults aged 75 years or older effectiveness of full vaccination for preventing hospitalizations was 85%.[23]

All adults

A case-control analysis among 3689 adults aged 18 years or older who were hospitalized at 21 US hospitals across 18 states during March 11 to August 15, 2021, among adults without immunocompromising conditions, vaccine effectiveness against COVID-19 hospitalization was 71%.[27] A comparative effectiveness US study across

multistate Mayo Clinic Health System between February 27 and July 22, 2021, of 8889 vaccinated persons and 88,898 unvaccinated persons (mean age, 52.4 years and 51.7, respectively) found a vaccine effectiveness of 73.6% (95% CI, 65.9%–79.9%) and a 3.73-fold reduction in SARS-CoV-2 infections.[30]

NEED FOR ADDITIONAL DOSES BEYOND PRIMARY SERIES ("BOOSTER DOSES")

The initial large-scale vaccinations against COVID-19 occurred less than 1 year before the drafting of this publication. Data regarding the long-term durability of clinical protection are rapidly emerging. Nevertheless, it has been repeatedly observed that neutralizing antibody titers wane, albeit with some variation by product. Titers induced by the Janssen (Ad26.COV2.S) vaccine seem lower but more stable over time, whereas neutralizing titers induced by the mRNA vaccines are initially higher but seem to decline with a steeper slope.[31] There seem to be subtle differences in the durability of clinical protection, with the Moderna (mRNA-1273) vaccine appearing to provide a slightly longer period of protection when compared with the Pfizer (BNT162b2) or Janssen (Ad26.COV2.S) vaccines.[32] Neutralizing antibody titers were a clear surrogate of protection observed in the initial randomized trial of the Moderna (mRNA-1273) product.[33] In combination with the observation that there are emerging data suggesting a waning of clinical immunity[32] and the observation that boosting with any product leads to an increase in antibody titers,[34] a mass-scale booster program was initiated in the United States toward the end of 2021.

The FDA authorized a booster dose for all persons regardless of primary series. In addition, the CDC does not differentiate their recommendations for a booster based on the initial product or platform. Finally, it is important to note that the approved dose of the booster is different from the dose approved for the primary series with respect to the Moderna (mRNA-1273) vaccine, where the dose is half of the initial dose. The Pfizer (BNT162b2) dose is the same as the primary series, and the Janssen booster dose (Ad26.COV2.S) is the same dose as the initial series. The reduced dose of the mRNA was selected to relieve pressure on manufacturing capacity and also to potentially reduce reactogenicity.

SUMMARY

The degree of clinical protection against COVID-19 provided by vaccination remains an incredible triumph of modern science. Analysis of data generated from "real-world" vaccination cohorts have recapitulated the striking degree of efficacy of vaccination against clinical disease, especially severe disease, observed in randomized controlled trials. Extremely rare severe adverse events, such as myocarditis, are much more likely to occur with clinical COVID-19 than after vaccination. Even for persons with documented anaphylaxis to a vaccine component, alternative vaccination strategies exist. Although there may be subtle differences with respect to the duration of protection against mild illness conferred by various vaccine products, these differences pale in comparison to the difference between the unvaccinated and those with only immunity following natural infection. The emergence of the Omicron variant has been associated with substantial immune escape, and the full degree of loss of protection against clinical disease is not yet clear at the time this article was prepared. It is clear, however, that substantial protection against severe disease has been maintained with vaccination, and it is clear that vaccination remains the best method for preventing severe disease.

CLINICS CARE POINTS

- Even for persons with documented anaphylaxis to a vaccine component, alternative vaccination strategies exist.
- There may be subtle differences with respect to the duration of protection against mild illness conferred by various vaccine products, these differences pale in comparison to the difference between the unvaccinated and those with only immunity following natural infection.
- The degree of clinical protection against COVID-19 provided by vaccination remains an incredible triumph of modern science.

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