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COVID-19 vaccine insights: The news beyond the headlines

Here is key intelligence on the recommended primary series, boosters, breakthrough infection, adverse events, special population vaccination, vaccine myths, and what the future might hold.

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PRACTICE RECOMMENDATIONS

› *Vaccinate all adults (≥ 18 years) against COVID-19, based on recommendations for the initial series and boosters.* (A)

› *Vaccinate patients against COVID-19 with evidence-based assurance that doing so reduces disease-related risk of hospitalization, myocardial infarction, stroke, need for mechanical ventilation, and death.* (A)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

Worldwide and across many diseases, vaccines have been transformative in reducing mortality—an effect that has been sustained with vaccines that protect against COVID-19.[1] Since the first cases of SARS-CoV-2 infection were reported in late 2019, the pace of scientific investigation into the virus and the disease—made possible by unprecedented funding, infrastructure, and public and private partnerships—has been explosive. The result? A vast body of clinical and laboratory evidence about the safety and effectiveness of SARS-CoV-2 vaccines, which quickly became widely available.[2-4]

In this article, we review the basic underlying virology of SARS-CoV-2; the biotechnological basis of vaccines against COVID-19 that are available in the United States; and recommendations on how to provide those vaccines to your patients. Additional guidance for your practice appears in a select online bibliography, "COVID-19 vaccination resources," on page 338.

SARS-CoV-2 virology

As the SARS-CoV-2 virus approaches the host cell, normal cell proteases on the surface membrane cause a change in the shape of the SARS-CoV-2 spike protein. That spike protein conformation change allows the virus to avoid detection by the host's immune system because its receptor-binding site is effectively hidden until just before entry into the cell.[5,6] This process is analogous to a so-called lock-and-key method of entry, in which the key (ie, spike protein conformation) is hidden by the virus until the moment it is needed, thereby minimizing exposure of viral contents to the cell. As the virus spreads through the population, it adapts to improve infectivity and transmissibility and to evade developing immunity.[7]

After the spike protein changes shape, it attaches to an angiotensin-converting enzyme 2 (ACE-2) receptor on the host cell, allowing the virus to enter that cell. ACE-2 receptors are

located in numerous human tissues: nasopharynx, lung, gastrointestinal tract, heart, thymus, lymph nodes, bone marrow, brain, arterial and venous endothelial cells, and testes.[5] The variety of tissues that contain ACE-2 receptors explains the many sites of infection and location of symptoms with which SARS-CoV-2 infection can manifest, in addition to the respiratory system.

Basic mRNA vaccine immunology

Although messenger RNA (mRNA) vaccines seem novel, they have been in development for more than 30 years.[8]

mRNA encodes the protein for the antigen of interest and is delivered to the host muscle tissue. There, mRNA is translated into the antigen, which stimulates an immune response. Host enzymes then rapidly degrade the mRNA in the vaccine, and it is quickly eliminated from the host.

mRNA vaccines are attractive vaccine candidates, particularly in their application to emerging infectious diseases, for several reasons:

- They are nonreplicating.
- They do not integrate into the host genome.
- They are highly effective.
- They can produce antibody and cellular immunity.
- They can be produced (and modified) quickly on a large scale without having to grow the virus in eggs.

Vaccines against SARS-CoV-2

Two vaccines (from Pfizer-BioNTech [Comirnaty] and from Moderna [Spikevax]) are US Food and Drug Administration (FDA)–approved for COVID-19; both utilize mRNA technology. Two other vaccines, which do *not* use mRNA technology, have an FDA emergency use authorization (from Janssen Biotech, of Johnson & Johnson [Janssen COVID-19 Vaccine] and from Novavax [Novavax COVID-19 Vaccine, Adjuvanted]).[9]

Pfizer-BioNTech and Moderna vaccines. The mRNA of these vaccines encodes the entire spike protein in its pre-fusion conformation, which is the antigen that is replicated in the host, inducing an immune response.[10-12] (Recall the earlier lock-and-key analogy: This conformation structure ingeniously replicates the exposed 3-dimensional key to the host's immune system.)

The Janssen vaccine utilizes a viral vector (a nonreplicating adenovirus that functions as carrier) to deliver its message to the host for antigen production (again, the spike protein) and an immune response.

The Novavax vaccine uses a recombinant nanoparticle protein composed of the full-length spike protein.[13,14]

In this review, we focus on the 2 available mRNA vaccines, (1) given their FDA-authorized status and (2) because Centers for Disease Control and Prevention (CDC) recommendations indicate a preference for mRNA vaccination over viral-vectored vaccination. However, we also address key points about the Janssen (Johnson & Johnson) vaccine.

Efficacy of COVID-19 vaccines

The first study to document the safety and efficacy of a SARS-CoV-2 vaccine (the Pfizer-BioNTech vaccine) was published just 12 months after the onset of the pandemic.[10] This initial trial demonstrated a 95% efficacy in preventing symptomatic, laboratory-confirmed COVID-19 at 3-month follow-up.[10] Clinical trial data on the efficacy of COVID-19 vaccines have continued to be published since that first landmark trial.

Data from trials in Israel that became available early in 2021 showed that, in mRNA-vaccinated adults, mechanical ventilation rates declined strikingly, particularly in patients > 70 years of age.[15,16] This finding was corroborated by data from a surveillance study of multiple US hospitals, which showed that mRNA vaccines were > 90% effective in preventing hospitalization in adults > 65 years of age.[17]

Data published in May 2021 showed that the Pfizer-BioNTech and Moderna vaccines were 94% effective in preventing COVID-19-related hospitalization.[18] During the end of the Delta wave of the pandemic and the emergence of the Omicron variant of SARS-CoV-2, unvaccinated people were 5 times as likely to be infected as vaccinated people.[19]

In March 2022, data from 21 US medical centers in 18 states demonstrated that adults

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TABLE 1

FDA-authorized SARS-CoV-2 vaccines[21-24]

Manufacturer	FDA status	Mechanism	Efficacy (prevention of hospitalization or death)	Common adverse effects[a]
Pfizer-BioNTech[21]	Full authorization	mRNA	95%	Pain (80%), redness (5%), and swelling (5%) at injection site; fever (15%); chills (35%); myalgia (30%)
Moderna[22]				Pain (85%), redness (3%), and swelling (5%) at injection site; fever (17%); chills (48%); myalgia (61%)
Janssen[23]	Emergency use authorization	Viral vector	90%	Pain, redness, and swelling at injection site; fever; chills; myalgia
Novavax[24]		Recombinant protein nanoparticle	89%[b]	Pain, headache, fatigue, muscle pain

FDA, US Food and Drug Administration; mRNA, messenger RNA.

[a] Reported after a second dose of vaccine.

[b] Primary endpoint was virologically confirmed symptomatic disease of any severity.

who had received 3 doses of the vaccine were 94% less likely to be intubated or die than those who were unvaccinated.[16] A July 2022 retrospective cohort study of 231,037 subjects showed that the risk of hospitalization for acute myocardial infarction or for stroke after COVID-19 infection was reduced by more than half in fully vaccinated (ie, 2 doses of an mRNA vaccine or the viral vector [Janssen/Johnson & Johnson] vaccine) subjects, compared to unvaccinated subjects.[20] The efficacy of the vaccines is summarized in **TABLE 1**.[21-24]

Even in patients who have natural infection, several studies have shown that COVID-19 vaccination after natural infection increases the level and durability of immune response to infection and reinfection and improves clinical outcomes.[9,20,25,26] In summary, published literature shows that (1) mRNA vaccines are highly effective at preventing infection and (2) they augment immunity achieved by infection with circulating virus.

Breakthrough infection. COVID-19 mRNA vaccines are associated with breakthrough infection (ie, infections in fully vaccinated people), a phenomenon influenced by the predominant viral variant circulating, the level of vaccine uptake in the studied population, and the timing of vaccination.[27,28] Nevertheless, vaccinated people who experience breakthrough infection are much less likely to be hospitalized and die compared to those who are unvaccinated, and vaccination with an mRNA vaccine is more effective than immunity acquired from natural infection.[29]

Vaccine adverse effects: Common, rare, myths

Both early mRNA vaccine trials reported common minor adverse effects after vaccination (**TABLE 1**[21-24]). These included redness and soreness at the injection site, fatigue, myalgias, fever, and nausea, and tended to be more common after the second dose. These adverse effects are similar to common adverse effects seen with other vaccines. Counseling information about adverse effects can be found on the CDC website.[a]

Two uncommon but serious adverse effects of COVID-19 vaccination are myocarditis or pericarditis after mRNA vaccination and thrombosis with thrombocytopenia syndrome (TTS), which occurs only with the Janssen vaccine.[30,31]

Myocarditis and pericarditis, particularly in young males (12 to 18 years), and mostly after a second dose of vaccine, was reported in May 2021. Since then, several studies have shown that the risk of myocarditis is

[a] www.cdc.gov/coronavirus/2019-ncov/vaccines/index.html

slightly higher in males < 40 years of age, with a predicted case rate ranging from 1 to 10 excess cases for every 1 million patients vaccinated.[30,32] This risk must be balanced against the rate of myocarditis associated with SARS-CoV-2 infection.

A large study in the United States demonstrated that the risk of myocarditis for those who contract COVID-19 is 16 times higher than it is for those who are disease free.[33] Observational safety data from April 2022 showed that men ages 18 to 29 years had 7 to 8 times the risk of heart complications after natural infection, compared to men of those ages who had been vaccinated.[34] In this study of 40 US health care systems, the incidence of myocarditis or pericarditis in that age group ranged from 55 to 100 cases for every 100,000 people after infection and from 6 to 15 cases for every 100,000 people after a second dose of an mRNA vaccine.[34]

A risk–benefit analysis conducted by the Advisory Committee on Immunization Practices (ACIP) ultimately supported the conclusions that (1) the risk of myocarditis secondary to vaccination is small and (2) clear benefits of preventing infection, hospitalization, death, and continued transmission outweigh that risk.[35] Study of this question, utilizing vaccine safety and reporting systems around the world, has continued.

There is emerging evidence that extending the interval between the 2 doses of vaccine decreases the risk of myocarditis, particularly in male adolescents.[36] That evidence ultimately led the CDC to recommend that it might be optimal that an extended interval (ie, waiting 8 weeks between the first and second dose of vaccine), in particular for males ages 12 to 39 years, could be beneficial in decreasing the risk of myocarditis.

TTS. A population risk–benefit analysis of TTS was conducted by ACIP while use of the Janssen vaccine was paused in the United States in December 2021.[36] The analysis determined that, although the risk of TTS was largely in younger women (18 to 49 years; 7 cases for every 1 million vaccine doses administered), benefits of the vaccine in preventing death, hospitalization, and a stay in the intensive care unit (ICU)—particularly if vaccination was delayed or there was a high rate of community infection—clearly outweighed risks. (The CDC estimated an incidence of 2 cases of TTS with more than 3 million doses of Janssen vaccine administered; assuming moderate transmission kinetics, more than 3500 hospitalizations and more than 350 deaths were prevented by vaccination.[36]) Ultimately, after the CDC analysis was released, vaccination utilizing the Janssen product resumed; however, the CDC offered the caveat that the Janssen vaccine should be used only in specific situations[36] (eg, when there has been a severe reaction to mRNA vaccine or when access to mRNA or recombinant nanoparticle vaccine is limited).

Myths surrounding vaccination

Myth #1: SARS-CoV-2 vaccines contain tissue from aborted fetuses. This myth, which emerged during development of the vaccines, is often a conflation of the use of embryonic cell lines obtained decades ago to produce vaccines (a common practice—not only for vaccines but common pharmaceuticals and foods).[37] There are no fetal cells or tissue in any SARS-CoV-2 vaccines, and the vaccines have been endorsed by several faith organizations.[38]

Myth #2: SARS-CoV-2 vaccines can cause sterility in men and women. This myth originated from a report in early December 2020 seeking to link a similarity in a protein involved in placental–uterine binding and a portion of the receptor-binding domain antigen produced by the vaccine.[39] No studies support this myth; COVID-19 vaccines are recommended in pregnancy by the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine.[40,41]

Myth #3: mRNA SARS-CoV-2 vaccines alter a recipient's DNA. mRNA vaccines are broken down by cellular enzymes. They cannot be integrated into the host genome.[8]

Boosters and vaccine mix-and-match

As the COVID-19 pandemic persists, with new variants of concern emerging, it has also become clear that immunity wanes. In July 2021, the first report was published after a cluster of breakthrough infections occurred in a town in Massachusetts.[42] There was no

Even in patients who have natural infection, vaccination increases the level and durability of immune response to infection and reinfection and improves outcomes.

recommendation, at the time, for a booster; the Delta variant was the predominant circulating strain. In this outbreak, there were 469 cases, 74% of which were in people who had received 2 doses of an mRNA vaccine.[42] Five patients were hospitalized; none died.[42] A key takeaway from this outbreak was that vaccination prevented death, even in the face of fairly wide breakthrough infection.

Newer data show that, although vaccine effectiveness against hospitalization was greater than 90% for the first 2 months after a third dose, it waned to 78% by 4 months.[43] Published data, combined with real-world experience, show that boosters provide additional reduction in the risk of death and hospitalization. This has led to a recommendation that all patients ≥ 5 years of age receive a booster.[19,26,43-48] The CDC now recommends that people who are ages 12 years and older receive a bivalent booster (containing both wild-type and Omicron-variant antigens) ≥ 2 months after their most recent booster or completed series.

Vaccination with an mRNA vaccine is more effective than immunity acquired from natural infection.

Future booster recommendations will consider the durability of the immune response over time (measured against the original immunizing virus) and the mutation rate of the virus.[49]

Given the limited supply of vaccine early in the pandemic, and the potential for future limitations, there was early interest in studying so-called mix-and-match SARS-CoV-2 vaccination—that is, receiving one product as a first series and then a different product as a booster, also known as *heterologous booster vaccination*. Although it is preferred that the 2 doses of the primary series be of the same vaccine product, studies that have examined this question support heterologous boosting as an acceptable approach to protective immunity[50] (**TABLE 2**[51]).

Vaccination in special populations

Three groups of patients have unique host characteristics that are important to consider when providing COVID-19 vaccination in your practice: pregnant patients, children, and patients in the broad category of "immunocompromised status."

Pregnant patients with SARS-CoV-2 infection are more likely to be hospitalized and have a higher risk of a stay in the ICU and need for mechanical ventilation. In a study of the course of illness in symptomatic pregnant patients who were hospitalized, 16.2% were admitted to an ICU and 8.5% were mechanically ventilated.[52] CDC observational data have consistently supported the finding that (1) pregnant patients infected with SARS-CoV-2 are at increased risk of preterm labor and (2) their newborns are at increased risk of low birth weight and requiring admission to the neonatal ICU.[53]

A systematic review of 46 studies in pregnant and lactating patients showed no increased risk of adverse effects from COVID-19 vaccination.[54] Furthermore, data from multiple studies demonstrate that immunoglobulin G antibodies cross the placenta to protect the infant at birth (ie, are found in umbilical cord blood and neonatal blood) and are found in breast milk. The precise kinetics and durability of these antibodies are unknown.

Pregnant patients were initially excluded from vaccine trials (although there were some patients ultimately found to be pregnant, or who became pregnant, during the trial). Careful examination of vaccine safety and efficacy data has supported the American College of Obstetricians and Gynecologists and European Board and College of Obstetrics and Gynaecology (EBCOG) recommendation that all pregnant patients be vaccinated. Furthermore, EBCOG recommends vaccination during the period of breastfeeding.[55]

Children. A major challenge during the pandemic has been to understand (1) the effect that infection with SARS-CoV-2 has on children and (2) the role of children in transmission of the virus. Although most children with COVID-19 have mild symptoms, a few require hospitalization and mechanical ventilation and some develop life-threatening multisystem inflammatory syndrome.[56] In a large, retrospective study of more than 12,000 children with COVID-19, 5.3% required hospitalization and almost 20% of that subset were admitted to the ICU.[57]

Various hypotheses have been put forward to describe and explain the differences in disease expression between children and adults. These include:

- the absence of comorbidities often

TABLE 2

Vaccination schedule and booster indication, by age group and vaccine type[51]

Vaccine	Approved age	Primary series	Booster
Pfizer-BioNTech	6 mo-4 y	3 doses (3-8 wk between Doses 1 and 2, ≥ 8 wk between Doses 2 and 3), at a dose specific to their age	Not approved for this age group (at time of publication)
	5-11 y	2 doses (21 d apart), at a dose specific to their age	≥ 5 mo after completing initial series
	≥ 12 y	2 doses (3-8 wk apart[a])	≥ 5 mo after completing initial series
Moderna	6 mo-17 y	2 doses (4-8 wk apart), at a dose specific to their age	Booster not recommended for this group
	≥ 18 y	2 doses (28 d apart)	≥ 5 mo after completing initial series (Pfizer or Moderna preferred)
Janssen[b]	≥ 18 y	1 dose	2 mo after completing initial series (Pfizer or Moderna preferred)
Novavax	≥ 18 y	2 doses (3-8 wk apart)	Not approved
Pfizer-BioNTech	> 50 y	2 doses	*First booster* ≥ 5 mo after completion of initial series (Pfizer or Moderna preferred) *Second booster* ≥ 4 mo after first booster (Pfizer or Moderna preferred)
Pfizer-BioNTech	Immunocompromised[c] patients	3 doses Second dose ≥ 3 wk after first dose Third dose ≥ 4 wk after second dose	*First booster* ≥ 3 mo after third dose (Pfizer or Moderna preferred) *Second booster* ≥ 4 mo after first booster (Pfizer or Moderna preferred)

[a] Waiting the full 8 weeks between the first and second doses of the Pfizer-BioNTech vaccine might decrease the risk of myocarditis.

[b] Use the Janssen vaccine in select clinical situations only (eg, after a severe reaction to an messenger RNA [mRNA] vaccine or when access to an mRNA vaccine or recombinant nanoparticle vaccine is limited).

[c] Including (but not limited to) malignancy, chronic kidney disease, liver disease, chronic lung disease, dementia, diabetes, heart disease, HIV infection, history of organ or stem-cell transplant, and use of immunosuppressant medication

seen in adults
- evidence that pediatric patients might have reduced expression of ACE-2
- a more active T-cell response in infected children, due to an active thymus.[56]

Although the number of children affected by severe SARS-CoV-2 infection is less than the number of adults, there have been important trends observed in infection and hospitalization as different variants have arisen.[58] The Delta and Omicron variants have both been associated with a disturbing trend in the rate of hospitalization of pediatric patients, particularly from birth to 4 years—patients who were ineligible for vaccination at the time of the study.[58] Ultimately, these data, combined with multiple studies of vaccine effectiveness in this age group, have led to an emergency use authorization for the Pfizer-BioNTech vaccination in pediatric populations and a recommendation from the American Academy of Pediatrics that all children ages 6 months and older be vaccinated.[59,60]

Immunocompromised patients. Patients broadly classified as immunocompromised have raised unique concerns. These

COVID-19 vaccination resources

Interim clinical considerations for use of COVID-19 vaccines currently approved or authorized in the United States

Centers for Disease Control and Prevention
www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html

COVID-19 ACIP vaccine recommendations

Advisory Committee on Immunization Practices (ACIP)
www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/covid-19.html

***MMWR* COVID-19 reports**

Morbidity and Mortality Weekly Report
www.cdc.gov/mmwr/Novel_Coronavirus_Reports.html

A literature hub for tracking up-to-date scientific information about the 2019 novel coronavirus

National Center for Biotechnology Information of the National Library of Medicine
www.ncbi.nlm.nih.gov/research/coronavirus

Understanding COVID-19 vaccines

National Institutes of Health COVID-19 Research
https://covid19.nih.gov/treatments-and-vaccines/covid-19-vaccines

How COVID-19 affects pregnancy

National Institutes of Health COVID-19 Research
https://covid19.nih.gov/how-covid-19-affects-pregnancy

patients have conditions such as malignancy, primary or secondary immunodeficiency, diabetes, and autoimmune disease; are taking certain classes of medication; or are of older age.[61] Early in the pandemic, data showed that immunocompromised hosts could shed virus longer than hosts with an intact immune system—adding to their risk of transmitting SARS-CoV-2 and of viral adaptation for immune escape.[62] Antibody response to vaccination was also less robust in this group.

There are limited data that demonstrate a short-lived reduction in risk of infection (in that study, Omicron was the prominent variant) with a fourth dose of an mRNA vaccine.[63] Based on these data and FDA approval, the CDC recommends (1) an additional third primary dose and (2) a second booster for people who are moderately or severely immunocompromised. For those ages 50 years or older, a second booster is now required for their vaccination to be considered up to date.[b]

Predictions (or, why is a COVID-19 vaccine important?)

What does the future hold for our struggle with COVID-19? Perhaps we can learn lessons from the study of the 4 known seasonal coronaviruses, which cause the common cold and circulate annually.[64] First, only *relative immunity* is produced after infection with a seasonal coronavirus.[64] Studies of antibodies to seasonal coronaviruses seem to suggest that, although antibody titers remain high, correlation with decreased infection is lacking.[65] Second, a dominant strain or 2 emerges each season, probably as a result of genetic variation and selective pressure for immune escape from neutralizing antibodies or cellular immunity.

The complex relationship among competing immune response duration, emergence of viral immune escape, increasing viral transmissibility, and societal viral source control (through vaccination, masking, distancing, testing, isolation, and treatment) widens the confidence bounds on our estimates of what the future holds. Late in 2020, the CDC began reporting wastewater surveillance data as a method for monitoring, and predicting changes in, community spread.[66] During Spring 2022, the CDC reported an increase in detection of SARS-CoV-2 from a third of wastewater sampling sites around the United States. This observation coincided with (1) appearance of still more transmissible BA.2 and, later, BA.2.12.1 variants and (2) general relaxing of masking and social distancing guidelines, following the decline of the Omicron variant.

At approximately that time, application to the FDA for a fourth shot (or a second booster) by Pfizer-BioNTech had been approved for adults > 50 years of age, at > 4 months after their previous vaccination.[57] In view of warn-

[b] Visit www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html for more guidance on COVID-19 vaccination for immunocompromised patients.

ing signs from wastewater surveillance, priorities for vaccination should be to:

- increase uptake in the hesitant
- get boosters to the eligible
- prepare to tackle either seasonal or sporadic recurrence of COVID-19—whichever scenario the future brings.

As an example of how these priorities have been put into action, in September 2022, the FDA approved, and the CDC recommended, new bivalent boosters for everyone ≥ 12 years of age (Pfizer-BioNTech) or for all those ≥ 18 years of age (Moderna), to be administered ≥ 2 months after receipt of their most recent booster or primary series. JFP

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Boosters provide additional reduction in the risk of death and hospitalization, which led to a recommendation that all patients ≥ 5 years of age receive a booster.

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