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COVID-19: Vaccines

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INTRODUCTION

Vaccines to prevent SARS-CoV-2 infection are considered the most promising approach for curbing the COVID-19 pandemic. Several COVID-19 vaccines are available globally. The World Health Organization (WHO) maintains an updated list of vaccine candidates under evaluation [1].

This topic will cover vaccines for SARS-CoV-2, with a focus on vaccines available in the United States. Other aspects related to prevention of COVID-19 are discussed in detail elsewhere. (See "COVID-19: Epidemiology, virology, and prevention", section on 'Prevention'.)

GENERAL PRINCIPLES

- **Pace of COVID-19 vaccine development** – Although COVID-19 vaccine development has been accelerated, each vaccine that has received emergency use listing by the World Health Organization (WHO; which includes those that have been authorized or approved in the United States) has gone through the standard preclinical and clinical stages of development. Safety criteria have remained stringent; data safety and monitoring committees (DSMCs) composed of independent vaccine experts and study sponsors assess adverse events that are reported in each phase of clinical study and approve advancement to the next phase.

- **Calculation of vaccine efficacy** – Vaccine efficacy in percent is the reduction in disease incidence among those who received vaccine versus those who received the control

product and is calculated with the following formula:

  - ([attack rate in the unvaccinated – attack rate in the vaccinated]/attack rate in the unvaccinated) x 100, often abbreviated as ([ARU – ARV]/ARU) x 100

- **Antigenic target** – The major antigenic target for COVID-19 vaccines is the surface spike protein (figure 1). It binds to the angiotensin-converting enzyme 2 (ACE2) receptor on host cells and induces membrane fusion (figure 2) [2]. Antibodies binding to the receptor-binding domain of the SARS-CoV-2 spike protein can prevent attachment to the host cell and neutralize the virus [3].

- **Vaccine platforms** – COVID-19 vaccines have been and are being developed using several different platforms (figure 3) [3]. Some of these are traditional approaches, such as inactivated virus or live attenuated viruses, which have been used for inactivated influenza vaccines and measles vaccine, respectively. Other approaches employ newer platforms, such as recombinant proteins (used for human papillomavirus vaccines) and vectors (used for Ebola vaccines). Some platforms, such as RNA and DNA vaccines, had never been employed in a licensed vaccine. General descriptions of the different platforms used for COVID-19 vaccines are presented in the table (table 1).

- **Site of delivery and immune response** – COVID-19 vaccines have been demonstrated to elicit a sufficient neutralizing response to protect against COVID-19. The site of vaccine delivery may impact the character of the immune response [3]. Natural respiratory infections elicit both mucosal and systemic immune responses. Most respiratory virus vaccines, however, are administered intramuscularly (or intradermally) and elicit primarily a systemic immune response, with less robust protection in the upper respiratory mucosa than after natural infection. Some live attenuated respiratory virus vaccines can be administered intranasally, approximating natural infection, and these may elicit additional mucosal immune responses, although they typically do not induce as high of a systemic antibody response as inactivated vaccines administered systemically do [4,5]. Live attenuated COVID-19 vaccines administered to the respiratory tract are under development.

- **Vaccine-enhanced disease** – Animal studies of certain vaccines for SARS-CoV-1 and MERS-CoV had raised concerns for enhanced disease with vaccination; after challenge with wild-type virus, some previously vaccinated animals developed non-neutralizing antibody and Th2 cell responses that were associated with eosinophilic lung inflammation [6-8]. No enhanced disease was seen in any human studies. Nevertheless, specific immunologic parameters were proposed for animal and human studies to reduce the risk of enhanced

disease with COVID-19 vaccines [9]. These include criteria for neutralizing antibody and Th1-polarized cellular immune responses.

APPROACH TO VACCINATION IN THE UNITED STATES

Available vaccines — In the United States, four COVID-19 vaccines are available:

- Two mRNA vaccines – Each mRNA vaccine has a monovalent formulation (antigenic target is based on the original SARS-CoV-2 strain) and a bivalent formulation (antigenic target is based on the original SARS-CoV-2 strain and the BA.4/BA.5 Omicron subvariants):

  - BNT162b2 **(Pfizer-BioNTech COVID-19 vaccine)** – This is a monovalent vaccine approved by the US Food and Drug Administration (FDA) for persons aged 12 years and older and is available under emergency use authorization (EUA) for children 6 months to 11 years of age [10].

    The bivalent formulation (Pfizer-BioNTech COVID-19 vaccine, bivalent [Original and Omicron BA.4/BA.5]) is authorized as a booster dose for individuals aged 12 years or older [11].

  - mRNA-1273 **(Moderna COVID-19 vaccine)** – This is a monovalent vaccine approved by the FDA for persons aged 18 years and older and is available under EUA for children 6 months to 17 years of age [12].

    The bivalent formulation (Moderna COVID-19 vaccine, bivalent [Original and Omicron BA.4/BA.5]) is authorized as a booster dose for individuals aged 18 years or older [13].

- An adjuvanted recombinant protein vaccine (monovalent):

  - **NVX-CoV2373 (Novavax COVID-19 vaccine)** – This is available under EUA for individuals aged 12 years or older [14].

- An adenoviral vector vaccine (monovalent):

  - Ad26.COV2.S **(Janssen/Johnson & Johnson COVID-19 vaccine)** – This is available under EUA for individuals aged 18 years or older who cannot or elect not to use an mRNA vaccine [15].

Indications and vaccine selection — We recommend COVID-19 vaccination for all individuals aged six months and older.

For individuals who are eligible for any COVID-19 vaccine, we suggest an mRNA vaccine (BNT162b2 [Pfizer COVID-19 vaccine] or mRNA-1273 [Moderna COVID-19 vaccine]) or NVX-CoV2373 (Novavax COVID-19 vaccine) rather than Ad26.COV2.S (Janssen/Johnson & Johnson COVID-19 vaccine). Extensive data supporting the use of mRNA vaccines have accumulated since their availability. Less data on safety and efficacy of NVX-CoV2373 are available, but it is also highly effective and may be an attractive option for individuals with concerns about the novelty of the mRNA vaccine platform (table 1). We reserve Ad26.COV2.S for individuals who have contraindications or no access to other COVID-19 vaccines, in agreement with the Centers for Disease Control and Prevention (CDC) and the terms of the EUA for Ad26.COV2.S (see 'Contraindications and precautions (including allergies)' below). Nevertheless, if other vaccines are not options, we recommend vaccination with Ad26.COV2.S rather than forgoing COVID-19 vaccination.

- **Rationale for vaccine recommendations** – Vaccines available in the United States are highly effective, substantially reduce the risk of COVID-19, especially severe/critical disease, and have been associated with substantial reductions in COVID-19-associated hospitalizations and deaths [16-23], even in the context of variants that partially evade vaccine-induced immune responses. Hospitalization and mortality rates for COVID-19 have been consistently higher among unvaccinated compared with vaccinated individuals, with or without booster doses [24]. In addition to direct reductions in COVID-19-associated morbidity and mortality, vaccination has been associated with lower non-COVID-19 mortality rates, supporting evidence that COVID-19 vaccination does not increase the risk of death [25]. Details on the efficacy and safety of the individual vaccines are discussed elsewhere. (See 'Immunogenicity, efficacy, and safety of select vaccines' below and 'Waning effectiveness over time and with variants of concern' below.)

  The preference for mRNA vaccines over Ad26.COV2.S is based on a more favorable risk-benefit profile with the mRNA vaccines. Ad26.COV2.S has been associated with thrombosis with thrombocytopenia and possibly Guillain-Barre syndrome, and the mRNA vaccines have been associated with myocarditis. The risks of these events are extremely small, and the benefits of all the vaccines outweigh them. However, cases of vaccine-associated thrombosis with thrombocytopenia and Guillain-Barre syndrome have been more severe with greater morbidity compared with cases of vaccine-associated myocarditis. Potential recipients of any vaccine should be aware of the specific risks, which are discussed in detail elsewhere. (See 'Specific safety concerns' below.)

  Additionally, although precise comparative efficacy is uncertain because the different vaccines have not been compared directly in trials, limited evidence suggests that mRNA

vaccines may be more effective than Ad26.COV2.S, including against severe infection, and mRNA-1273 may be slightly more effective than BNT162b2 [26-31].

- In several observational studies, vaccine effectiveness associated with two doses of the mRNA vaccines is higher than that with one dose of Ad26.COV2.S [16,26,32-34]. As an example, in a case control study of 3689 immunocompetent adults hospitalized for COVID-19, estimated effectiveness against COVID-19-related hospitalization was 93 and 88 percent for mRNA-1273 and BNT162b2, respectively, compared with 71 percent for Ad26.COV2.S. Although the analysis adjusted for age, sex, admission date, geographic region, and race, the contribution of these and other unmeasured confounders, such as variable exposure risk, to the apparent differences in effectiveness is uncertain.

- Several observational studies also suggest that mRNA-1273 vaccine effectiveness is slightly higher than that of BNT162b2, although it is unclear whether there is a clinically significant difference [26-31,35]. In a study from the United States that compared over 400,000 veterans who received either mRNA-1273 or BNT162b2, mRNA-1273 was associated with lower rates of documented infection, symptomatic COVID-19, and associated hospitalization over 24 weeks, but the absolute differences were low (differences of 1.23, 0.44, and 0.55 cases per 1000 people, respectively) [28]. Safety of the mRNA vaccines in the same cohort was largely comparable, with only small differences in serious adverse events of uncertain clinical significance [36].

Because it has not been available for as long as the other vaccines, data on NVX-CoV2373 are more limited, although large randomized trials support its efficacy; there may be a risk for myocarditis with this vaccine as well. (See 'NVX-CoV2373 (Novavax COVID-19 vaccine)' below.)

Dose and interval — Vaccine dosing and intervals are also listed in the table (table 2).

Primary vaccine series

Adults and adolescents age 12 years and older — Monovalent vaccines are used for all primary vaccine series. Dosing for individuals ≥12 years of age is as follows:

- BNT162b2 **(Pfizer-BioNTech COVID-19 vaccine, an mRNA vaccine)** – Two intramuscular doses of 30 mcg given three to eight weeks apart (figure 4) [10].

  For individuals with certain immunocompromising conditions (table 3), a third dose is given at least 28 days after the second (figure 5). (See 'Immunocompromised individuals' below.)

- mRNA-1273 **(Moderna COVID-19 vaccine, an mRNA vaccine)** – Two intramuscular doses of 100 mcg given four to eight weeks apart (figure 4) [12].

  For individuals with certain immunocompromising conditions (table 3), a third dose is given at least 28 days after the second (figure 5). (See 'Immunocompromised individuals' below.)

- **NVX-CoV2373 (Novavax COVID-19 vaccine, an adjuvanted recombinant protein vaccine)** – Two intramuscular doses of 5 mcg spike protein/50 mcg adjuvant given three to eight weeks apart (figure 4) [14].

  NVX-CoV2373 is not yet authorized to be given as an additional primary series dose for individuals with immunocompromising conditions.

- Ad26.COV2.S **(Janssen COVID-19 vaccine, also referred to as the Johnson & Johnson vaccine, an adenoviral vector vaccine)** – This vaccine is only authorized for individuals ≥18 years of age and is reserved for individuals who cannot receive one of the other COVID-19 vaccines. (See 'Indications and vaccine selection' above.)

  It is given as one intramuscular dose of $5x10^{10}$ viral particles (0.5 mL) (figure 4) [15]. For individuals with certain immunocompromising conditions (table 3), an additional dose with an mRNA monovalent vaccine is recommended at least four weeks later to complete a primary series (figure 5) [12]. (See 'Immunocompromised individuals' below.)

The same vaccine, if available, is generally used to complete the primary series.

Although the mRNA vaccines and NVX-CoV2373 were originally evaluated with a three- to four-week interval between the two primary series doses, extending that interval to eight weeks may be preferable for young, healthy adults who do not need to maximize protection within a shorter period of time. Specifically, an eight-week or longer interval has been associated with a lower risk of vaccine-associated myocarditis than a one month or shorter interval, which is most relevant for males 12 to 39 years old [37] (see 'Myocarditis' below). Additionally, some studies have suggested that increasing the interval between the two doses of the primary series (eg, separating them by 6 to 14 weeks rather than 3 to 4 weeks) is associated with higher titer antibody responses [38,39] and slightly greater vaccine effectiveness [40,41].

Children younger than 12 years of age — Monovalent vaccines are used for all primary vaccine series unless otherwise specified below. Dosing for children <12 years of age is as follows:

- BNT162b2 **(Pfizer-BioNTech COVID-19 vaccine, an mRNA vaccine)**

- For children 5 to 11 years of age:
  - Primary series – Two intramuscular doses of 10 mcg are given three weeks to eight weeks apart. For individuals in this age group with certain immunocompromising conditions (table 3), the FDA has authorized and the CDC suggests a third primary series dose, given at least 28 days after the second (figure 5) [42]. (See 'Immunocompromised individuals' below.)
- For children six months to four years of age:
  - Primary series – Three intramuscular doses. The first two doses are each 3 mcg of the monovalent vaccine, given three to eight weeks apart. The third dose is with 3 mcg of the bivalent vaccine (Pfizer-BioNTech COVID-19 vaccine, bivalent), given at least eight weeks after the second [43].

- mRNA-1273 **(Moderna COVID-19 vaccine, an mRNA vaccine)**
  - For children 6 to 11 years of age:
    - Primary series – Two intramuscular doses of 50 mcg given four to eight weeks apart. For individuals in this age group with certain immunocompromising conditions (table 3), the FDA has authorized and the CDC suggests a third primary series dose, given at least four weeks after the second (figure 5) [42]. (See 'Immunocompromised individuals' below.)
  - For children six months to five years of age:
    - Primary series – Two intramuscular doses of 25 mcg given four to eight weeks apart. For individuals in this age group with certain immunocompromising conditions (table 3), the FDA has authorized and the CDC suggests a third primary series dose, given at least four weeks after the second (figure 5) [42]. (See 'Immunocompromised individuals' below.)

The CDC recommends that children should receive the dose and formulation authorized for their age on the day of vaccine receipt, regardless of weight [42]. If they age into the next age group before the next primary series dose is due, they should complete the primary series with the dose and formulation authorized for the older age group. However, COVID-19 vaccine authorization for these age groups allows for such individuals to receive the entire primary series at either the dose authorized for their current age range or the dose authorized for the age they will be.

Additional considerations regarding COVID-19 vaccination in children are discussed elsewhere. (See 'Children' below.)

Booster dose

Individuals age five years and older — For all individuals ≥5 years of age who have completed a primary series of a COVID-19 vaccine (including those who have already received additional booster doses with a monovalent vaccine), the CDC recommends a booster dose with one of the bivalent mRNA vaccines at least two months after the last vaccine dose. Monovalent mRNA vaccines are no longer authorized for booster doses.

- **Dosing** – The dose depends on the patient age:
  - **Pfizer-BioNTech COVID-19 vaccine, bivalent (Original and Omicron BA.4/BA.5)**
    - For individuals ≥12 years of age: A single intramuscular 30 mcg booster dose [11].
    - For individuals 5 to 12 years of age: A single intramuscular 10 mcg booster dose [44].
  - **Moderna COVID-19 vaccine, bivalent (Original and Omicron BA.4/BA.5)**
    - For individuals ≥12 years of age: A single intramuscular 50 mcg booster dose [13].
    - For individuals 6 to 12 years of age: A single intramuscular 25 mcg booster dose [13].
    - For individuals 5 years of age: A single intramuscular 10 mcg booster dose.

  The recommendation for the bivalent booster dose replaces previous booster recommendations for individuals ≥5 years old, which had included at least one monovalent booster dose for all and an additional booster dose for those who were ≥50 years old or had an immunocompromising condition.

  The rationale and evidence supporting the bivalent booster vaccines are discussed elsewhere. (See 'Bivalent mRNA vaccine booster effectiveness and immunogenicity' below.)

- **Optimal timing** – Although individuals are eligible to receive a bivalent booster dose at least two months after their last vaccine dose, the optimal timing after this interval is uncertain. We suggest that individuals who have immunocompromising conditions (table 3) or would otherwise be at high risk of severe disease (eg, because of multiple medical comorbidities) receive the booster as soon as they are eligible. We also suggest that individuals living in a region with high or increasing rates of SARS-CoV-2 transmission

receive the booster once eligible. Although it is uncertain if waiting longer to receive the booster dose (eg, at least three months after the last vaccine dose) improves immunogenicity or efficacy or reduces the risk of adverse effects, this could be a reasonable option for other individuals, in particular for healthy adolescent and young adult males, the population most at risk for vaccine-associated myocarditis. (See 'Myocarditis' below.)

Timing of vaccination following SARS-CoV-2 infection is discussed elsewhere. (See 'History of SARS-CoV-2 infection' below.)

For individuals 18 years or older who have received a primary vaccine series but no prior booster dose and are unable or unwilling to receive an mRNA vaccine, a single dose of NVX-CoV2373 (Novavax vaccine, 5 mcg spike protein/50 mcg adjuvant) can be used as a booster dose at least six months after the last primary series dose [42,45].

Children six months to four years old — CDC recommendations on booster doses for children 6 months to 4 years old depend on the primary series received [42,43].

- For those who received mRNA-1273 (Moderna COVID-19 vaccine) – A single intramuscular 10 mcg booster dose of the bivalent vaccine (Moderna COVID-19 vaccine, bivalent) at least two months after completing the primary series.

- For those who received BNT162b2 (Pfizer-BioNTech COVID-19 vaccine) – A booster dose has not been authorized if the three-dose primary series has been completed. However, for those who have not yet completed the vaccine series, a bivalent vaccine (Pfizer-BioNTech COVID-19 vaccine, bivalent) dose has been authorized as the third dose of the primary series. (See 'Children younger than 12 years of age' above.)

Support for bivalent vaccines in young children comes from immunogenicity bridging studies with monovalent vaccines and immunogenicity studies of the bivalent vaccine in other age groups. (See 'Children' below and 'Bivalent mRNA vaccine booster effectiveness and immunogenicity' below.)

Other administration issues

Technique and potential administration errors — In adults and adolescents, intramuscular vaccines are typically injected into the deltoid. Proper injection technique to reduce the risk of shoulder injury involves injection at a 90° angle into the central, thickest part of the deltoid (figure 6). (See "Standard immunizations for nonpregnant adults", section on 'Technique'.)

Additional details on administration can be found on the CDC website. The following table details CDC recommendations on the management of vaccine administration errors (table 4).

Mixing vaccine types

- **Completing the primary series** – For the mRNA and adjuvant recombinant protein vaccines, the CDC suggests that the primary series be completed with the same vaccine, if possible [42]; there are insufficient data to inform the efficacy and safety of mixing vaccines for the primary series. If extenuating circumstances result in needing to complete the series with a different vaccine (ie, because of unavailability, new contraindication), the CDC recommends that the second dose be given at least four weeks after the first. If two different vaccine products are used to complete the series, no additional doses of a COVID-19 vaccine are recommended (table 4). The same principles apply to children aged six months to four years who are started on a three-dose primary series and, presumably, for patients with immunocompromising conditions that warrant a third mRNA vaccine dose.

- **Providing booster doses** – In the United States, bivalent mRNA vaccines are used for booster doses. Those who received an mRNA vaccine for the primary series can use either one of the bivalent mRNA vaccines (if authorized for their age group); they do not have to use the bivalent vaccine from the same manufacturer. (See 'Dose and interval' above.)

  For those who received a non-mRNA vaccine for the primary series, studies indicate robust immunogenicity with an mRNA booster dose (ie, a heterologous boost) [46-48] and greater effectiveness than with homologous boosting [49-51]. As an example, in a study of nearly 5 million United States veterans, receipt of an mRNA vaccine boost after a primary Ad26.COV2.S dose was associated with a lower risk of infection than receipt of an Ad26.COV2.S boost (adjusted rate ratio 0.49); for mRNA vaccine recipients, there was not a substantial difference in infection rates in recipients of a homologous mRNA boost versus a heterologous mRNA boost [49]. Immunogenicity studies support these findings. In a randomized trial of individuals who had received a primary Ad26.COV2.S series, an mRNA-1273 (Moderna COVID-19 vaccine) boost resulted in higher binding and neutralizing antibody levels than a BNT162b2 (Pfizer COVID-19 vaccine) boost, and levels with both mRNA vaccine boosts were higher than with another Ad26.COV2.S dose [47]. No safety concerns were identified; the frequency and duration of systemic symptoms (eg, fever, chills, myalgias) may be slightly higher with mRNA-1273 booster doses.

  Immunogenicity with a heterologous bivalent vaccine boost is unknown but likely similar to the effect seen with monovalent mRNA vaccine boosting.

Studies from other countries using different vaccines to complete a series (eg, ChAdOx1 nCoV-19/ADZ122 followed by BNT162b2 or mRNA-1273) suggests a more robust, broad, and durable immune response with certain heterologous vaccine combinations, although in some cases there is a higher rate of systemic reactions (fever, fatigue, headaches, myalgias) compared with using the same vaccine for both doses [52-56].

Timing with relation to non-COVID-19 vaccines — The CDC specifies that COVID-19 vaccines can be administered at any time in relation to most other non-COVID-19 vaccines, and if needed, can be administered simultaneously with other vaccines [42].

- **Coadministration** – When coadministered, each vaccine should be injected in different sites separated by at least one inch (and vaccines that are associated with local reactions should ideally be injected in a different limb than COVID-19 vaccines). Limited data suggest that coadministration of COVID-19 vaccines with certain other vaccines is likely safe. In a randomized trial, frequency of adverse effects and immunogenicity were largely similar when a COVID-19 vaccine (BNT162b2 or ChAdOx1) was given concomitantly with either an influenza vaccine or placebo [57].

- **Additional considerations with orthopoxvirus vaccination** – For individuals who have received an orthopoxvirus vaccine to prevent mpox (formerly known as monkeypox), particularly adolescent or young adult males, the CDC suggests that it is reasonable to defer COVID-19 vaccination for four weeks because of the uncertain risk of myocarditis with closely spaced administration [42]. However, recent COVID-19 vaccination should not delay orthopoxvirus vaccination if indicated, given the potential health burden of mpox in the at-risk population.

Limited role for post-vaccination testing — Unless indicated to evaluate for suspected infection, there is no role for routine post-vaccination testing for COVID-19. Specifically, serologic testing following vaccination to confirm an antibody response or to determine whether to give additional doses of vaccine (eg, booster doses) is not indicated. Many serologic tests will not detect the type of antibodies elicited by vaccination. This is discussed elsewhere. (See "COVID-19: Diagnosis", section on 'Testing following COVID-19 vaccination'.)

Some side effects of vaccination overlap with symptoms of COVID-19. Systemic reactions (eg, fever, chills, fatigue, headache) that occur within the first day or two after vaccination and resolve within a day or two are consistent with a reaction to the vaccine. However, respiratory symptoms or systemic symptoms that occur after the first couple days following vaccination or that last several days could be indicative of COVID-19 and warrant testing. (See "COVID-19: Diagnosis", section on 'Choosing an initial diagnostic test'.)

Considerations for special populations

History of SARS-CoV-2 infection — We suggest eligible individuals with a history of SARS-CoV-2 infection receive a COVID-19 vaccine; pre-vaccination serologic screening to identify prior infection is not recommended [42]. All recommended primary series and booster doses should be given, even if SARS-CoV-2 infection is diagnosed after vaccination has been initiated.

- **Timing of vaccination** – Individuals with recent, documented SARS-CoV-2 infection (including those who are diagnosed after initiating a vaccine series) should have at least recovered from acute infection and met criteria for discontinuation of isolation precautions before receiving a vaccine dose. Additionally, given the low risk of reinfection soon after prior infection, it is reasonable for individuals with SARS-CoV-2 infection to wait to receive a vaccine dose until three months after infection [42]. This applies to receipt of any primary series or booster dose. Potential reasons not to delay the vaccine dose in this population include high risk for severe infection, high rates of community transmission, and circulating variants associated with a high risk of reinfection. (See 'Other administration issues' above.)

- **Individuals with a history of MIS** – For individuals who had SARS-CoV-2 infection complicated by multisystem inflammatory syndrome (MIS), the decision to vaccinate should be individualized and weigh the risk of exposure, reinfection, and severe disease with infection against the uncertain safety of vaccination in such individuals. Given the hypothesis that MIS is associated with immune dysregulation precipitated by SARS-CoV-2 infection, it is unknown if a SARS-CoV-2 vaccine could trigger a similar dysregulated response. Nevertheless, the benefits of vaccination may outweigh the risk among those with a history of MIS if they have recovered clinically, had MIS ≥90 days previously, and are at increased risk for SARS-CoV-2 exposure, and if the MIS was not associated with COVID-19 vaccination [42]. In a study of 186 individuals ≥5 years old with a history of MIS ≥90 days prior to vaccine receipt, the side effect profile of mRNA vaccination was similar to that in the general population; no cases of myocarditis or recurrent MIS were observed [58].

Vaccination is still beneficial in many patients with a history of SARS-CoV-2 infection. Vaccination appears to further boost antibody levels and cell-mediated responses in those with past infection and might improve the durability and breadth of protection [59-61]. In multiple observational studies of individuals with prior infection, vaccination has been associated with a lower risk of subsequent reinfection and hospitalization [62-69]; it has also been associated with a lower risk of breakthrough infection compared with vaccination in individuals without prior infection [70,71].

Vaccination has been associated with greater protection against hospitalization for COVID-19 compared with prior infection in some studies [72]. However, one study suggested that when Delta variant was prevalent, prior infection was associated with greater protection against COVID-19-related hospitalization than vaccination, although vaccination was still protective; estimates were age adjusted, but this study did not account for other potential confounders that may affect hospitalization risk (eg, comorbidities, exposure risk) [73].

Among individuals who have persistent symptoms following acute COVID-19, vaccination has been associated with a higher likelihood of symptom improvement compared with no vaccination, according to a systematic review by the United Kingdom Health Security Agency; however, for most individuals, symptoms remain unchanged regardless of vaccination [74].

Individuals with a history of SARS-CoV-2 may be more likely to experience local and systemic adverse effects (eg, fevers, chills, myalgias, fatigue) after a first vaccine dose than SARS-CoV-2-naïve individuals [42,75,76]. This is not a contraindication or precaution for subsequent vaccine doses.

Recent SARS-CoV-2 exposure — Individuals with a known SARS-CoV-2 exposure should receive COVID-19 vaccination, as recommended for the general population. However, such individuals who are in the community should wait until they have completed their post-exposure quarantine period to avoid inadvertent exposures to others in the event of infection [42]. Individuals who are exposed to SARS-CoV-2 in a congregate residential setting can receive COVID-19 vaccination without delay.

Given that the time needed to generate a protective immune response following vaccination exceeds the mean incubation period of SARS-CoV-2, post-exposure vaccination would likely not reduce the risk of infection following that specific exposure.

Immunocompromised individuals — We suggest that eligible individuals who have an immunocompromising condition or are taking immunosuppressive agents undergo COVID-19 vaccination. Immunogenicity and effectiveness of COVID-19 vaccines appear lower in such individuals compared with the general population; nevertheless, the potential for severe COVID-19 in this population outweighs the uncertainties. Considerations for immunocompromised patients given the potential for reduced vaccine response include the following:

- **Additional vaccine dose in the primary series** – We agree with recommendations from the Advisory Committee on Immunization Practices (ACIP) that individuals with certain immunocompromising conditions who received a two-dose mRNA vaccine series receive a third dose (if possible, the same vaccine formulation should be used) as part of the primary vaccine series, administered at least 28 days after the second dose (figure 5)

[77]; for those who received Ad26.COV2.S, a dose of an mRNA vaccine is recommended at least 28 days later [42]. The vaccine dosage should be the same as that used for all primary series doses (eg, for mRNA-1273 [Moderna COVID-19 vaccine], the 100 mcg dose). (See 'Dose and interval' above.)

Immunocompromising conditions that warrant an additional primary series dose include active use of chemotherapy for cancer, hematologic malignancies, hematopoietic stem cell or solid organ transplant, advanced or untreated HIV infection with CD4 cell count <200 cells/microL, moderate or severe primary immunodeficiency disorder, and use of immunosuppressive medications (eg, mycophenolate mofetil, rituximab, prednisone >20 mg/day for >14 days) (table 3) [78]. This list is not exhaustive; other conditions, such as impaired splenic function [79], may also warrant an additional vaccine dose.

Several other countries, including France, Germany, and Israel, have made similar recommendations [80]. Patients with immunocompromising conditions should be advised to continue other protective measures regardless of the number of vaccine doses received, as immune response may not be optimal even with three doses.

In observational studies of immunocompromised individuals, receipt of three doses of mRNA vaccines is associated with higher vaccine effectiveness than two doses [81,82]. In studies of transplant recipients who received a third dose of mRNA vaccines, seroconversion rates were higher after the additional dose, although approximately 50 to 70 percent who were seronegative after two doses remained seronegative; adverse effects were similar to those reported after prior doses [83-87]. Receipt of an additional dose following three doses of an mRNA vaccine (akin to a booster dose after a three-dose primary series) has also been associated with improved seroconversion rates [88].

- **Timing immunosuppressive agents and vaccination** – Some expert groups recommend holding certain immunosuppressive agents around the time of vaccination or adjusting the timing of vaccination to account for receipt of such agents to try to optimize the vaccine response. As an example, for patients receiving rituximab, the American College of Rheumatology suggests scheduling vaccination so that the series is initiated approximately four weeks prior to the next scheduled rituximab dose and delaying administration of rituximab until two to four weeks after completion of vaccination, if disease activity allows [89]. (See "COVID-19: Care of adult patients with systemic rheumatic disease", section on 'COVID-19 vaccination while on immunosuppressive therapy'.)

- **Revaccination following certain immunosuppressing therapies** – For those who received COVID-19 vaccination prior to hematopoietic cell transplantation (HCT) or

chimeric antigen receptor (CAR)-T cell therapy, the CDC recommends repeat vaccination with a full primary series at least three months after the transplant or CAR-T administration [42]. For those who were vaccinated during a limited course of a B-cell-depleting therapy, repeat vaccination is suggested six months following therapy. All these patients meet criteria for receiving a three-dose primary series with the mRNA vaccines. (See "Immunizations in hematopoietic cell transplant candidates and recipients", section on 'COVID-19 vaccine'.)

- **Continued use of protective measures and potential pre-exposure prophylaxis** – We advise immunocompromised patients to maintain personal measures to try to minimize exposure to SARS-CoV-2 (eg, masking, distancing, avoiding crowds when possible) even after they have been vaccinated because of the potential for reduced vaccine effectiveness. Household and other close contacts of immunocompromised patients should be vaccinated.

  Immunocompromised patients who are at risk for suboptimal response to vaccination may be eligible for pre-exposure prophylaxis with monoclonal antibodies. This is discussed in detail elsewhere. (See "COVID-19: Epidemiology, virology, and prevention", section on 'Pre-exposure prophylaxis for selected individuals'.)

- **Limited role for post-vaccination serology** – At this time, antibody testing is not recommended to determine response to vaccination; precise immune correlates of protection remain uncertain [42]. Furthermore, heterogeneity in the accuracy of available serologic tests complicates interpretation of results. (See 'Limited role for post-vaccination testing' above.)

Data suggest that COVID-19 vaccines are effective in many immunocompromised patients, even in the context of the Omicron variant, although they are less so than in individuals without compromised immune systems [90-97]. In a cohort study of over 1 million individuals who had received at least one mRNA vaccine in Israel, vaccine effectiveness for symptomatic COVID-19 was 75 percent (95% CI 44-88) among immunocompromised patients compared with 94 percent (95% CI 87-97) overall [90]. Lower vaccine effectiveness against hospitalization for COVID-19 in immunocompromised patients has also been suggested by smaller case-control studies [91]. In studies of individuals hospitalized with COVID-19 despite vaccination, a high proportion (eg, 40 percent) have been immunocompromised [92].

In particular, transplant recipients and individuals taking B-cell-depleting agents have a suboptimal vaccine response [96,98-102]. Among transplant recipients, use of antimetabolites

(eg, mycophenolate mofetil, azathioprine) and a shorter time since transplantation have been associated with a higher rate of nonresponse.

Issues related to vaccination of specific immunocompromised populations are discussed in detail elsewhere:

- (See "COVID-19: Considerations in patients with cancer", section on 'COVID-19 vaccination'.)
- (See "COVID-19: Care of adult patients with systemic rheumatic disease", section on 'COVID-19 vaccination while on immunosuppressive therapy'.)
- (See "COVID-19: Issues related to solid organ transplantation", section on 'Vaccination'.)
- (See "Immunizations in patients with primary immunodeficiency", section on 'Issues related to SARS-CoV-2 vaccination'.)

Pregnant individuals — Vaccine recommendations for the general population extend to pregnant individuals as well. Data on safety and efficacy of COVID-19 vaccination in individuals who are pregnant or breastfeeding are discussed in detail elsewhere. (See "COVID-19: Overview of pregnancy issues", section on 'Vaccination in people planning pregnancy and pregnant or recently pregnant people'.)

Children — We recommend that eligible children undergo COVID-19 vaccination. Specifically, in the United States, the FDA has authorized and the CDC recommends BNT162b2 (Pfizer COVID-19 vaccine) or mRNA-1273 (Moderna COVID-19 vaccine) for children and adolescents aged six months and older based on evidence that efficacy and immunogenicity are as high as (or higher than) those in older individuals with rare serious adverse effects. Observational studies also indicate that vaccination is associated with reductions in COVID-19-related hospitalization, intensive care unit admission, death in adolescents, and reductions in hospitalization in younger children. For children under five years old, support for vaccine efficacy is primarily extrapolated from studies demonstrating that the neutralizing activity elicited by vaccination is comparable to levels associated with protection in older populations. These data and other data on the efficacy and safety of the specific vaccines are discussed elsewhere (see 'BNT162b2 (Pfizer-BioNTech COVID-19 vaccine)' below and 'mRNA-1273 (Moderna COVID-19 vaccine)' below). Dosing in children is also discussed elsewhere. (See 'Dose and interval' above.)

The individual benefit of COVID-19 vaccination in young children may be somewhat less than in adults because COVID-19 tends to be less severe in children than in adults. Nevertheless, the risk of the multisystem inflammatory syndrome in children (MIS-C) following acute infection, the potential for other sequelae of SARS-CoV-2 infection (eg, “long-COVID-19” and indirect effects

on mental health and education), the risk of severe disease in children with underlying medical conditions, and the desire to prevent COVID-19 of any severity in children remain compelling reasons for vaccination of children [103]. Furthermore, even with the lower risk of severe disease among children, the number of COVID-19 deaths among those 6 months to 11 years old during the pandemic exceeds the prevaccination era mortality rates of infections for which childhood vaccines are routinely provided (eg, rotavirus, meningococcal disease, varicella) [104,105].

The association of mRNA COVID-19 vaccines with myocarditis, particularly among male adolescents and young adults, has raised concern about this risk in younger children. However, data suggest that the risk is not higher than baseline [106]. No cases of myocarditis thought related to vaccine were reported in the trials of BNT162b2 or mRNA-1273 in young children [107,108]. In a review of the Vaccine Adverse Event Reporting System (VAERS) following administration of approximately 8.7 million doses of BNT162b2 to children aged 5 to 11 years in the United States, there were 11 verified reports of myocarditis in this age group [109]; no cases were reported following 1.5 million doses among children six months to five years of age [110]. As with other reported cases of mRNA COVID-19 vaccine-associated myocarditis, most cases were mild and of short duration. The benefits of COVID-19 vaccination in children are considered to exceed this risk [104,111]. (See 'Myocarditis' below.)

Given the hypothesis that MIS-C is associated with immune dysregulation precipitated by SARS-CoV-2 infection, similar immune-related side effects following vaccination in children are another concern. Vaccine trials in this age group have not identified a potential signal, although rare case reports of MIS in adults following vaccination highlight the importance of monitoring for this possible adverse effect [112]. Nevertheless, some evidence suggests that vaccination may protect against MIS-C [113,114]. In a study of 102 patients aged 12 to 18 years hospitalized with MIS-C, 95 percent were unvaccinated; of the 5 patients with MIS-C who had previously received primary series of BNT162b2, none required invasive respiratory or cardiovascular support [114]. The decision to vaccinate individuals with a history of MIS-C is discussed elsewhere. (See 'History of SARS-CoV-2 infection' above.)

Most vaccines for children are delivered by private health care providers, although many are purchased using federal or other government funds. The Vaccines for Children (VFC) program is an entitlement program for all ACIP-approved vaccines for eligible children through 18 years of age [115,116]. Eligible children include those on Medicaid, those who are completely uninsured, and American Indian/Alaskan Natives. Approximately 50 percent of children are covered by the VFC. In addition, federal grants to states can be used to purchase vaccines to cover other children. Since COVID-19 vaccines are free to all persons for whom the vaccines are

recommended, these funding mechanisms may be used with the COVID-19 vaccines that are licensed in children in addition to other funding sources.

Patient counseling

Expected adverse effects and their management

- **Common local and systemic reactions** – Vaccine recipients should be advised that side effects are common and include local and systemic reactions, including pain at the injection site, ipsilateral axillary lymph node enlargement, fever, fatigue, and headache. Local and systemic side effects may reflect a robust immune response, as some studies suggest that recipients who report symptoms have slightly higher post-vaccination antibody levels than those who did not [117,118]. Nevertheless, almost all immunocompetent recipients develop sufficiently high antibody levels, regardless of side effects. Among mRNA vaccines, BNT162b2 may be associated with slightly lower rates of local and systemic reactions compared with mRNA-1273 [119]. Rates of reactions for the distinct vaccines are discussed in detail elsewhere. (See 'BNT162b2 (Pfizer-BioNTech COVID-19 vaccine)' below and 'mRNA-1273 (Moderna COVID-19 vaccine)' below and 'Ad26.COV2.S (Janssen/Johnson & Johnson COVID-19 vaccine)' below.)

  Although analgesics or antipyretics (eg, nonsteroidal anti-inflammatory drugs [NSAIDs] or acetaminophen) can be taken if these reactions develop, prophylactic use of such agents before vaccine receipt is not recommended because of the uncertain impact on the host immune response to vaccination [42]. Although some data with other vaccines suggested a lower antibody response with prophylactic acetaminophen, the antibody responses to these vaccines remained in the protective range [120,121]. Aspirin is not recommended for individuals ≤18 years old because of the risk of Reye syndrome.

  Because of the risk of axillary lymph node enlargement following vaccination, some expert societies suggest postponing breast cancer screening mammography for several weeks post-vaccination if it cannot be performed beforehand. (See "COVID-19: Considerations in patients with cancer", section on 'Relative to radiologic imaging'.)

- **Syncope** – Syncope has been reported following receipt of other injectable vaccines, particularly among adolescents and young adults [122]. Monitoring is recommended for 15 to 30 minutes following COVID-19 vaccine receipt, and this may help reduce the risk of syncope-related injury. (See 'Monitoring for immediate reactions to vaccine' below.)

- **Rare adverse events** – Very rare vaccine-associated adverse events include anaphylaxis and myocarditis with the mRNA vaccines (BNT162b2 and mRNA-1273) and unusual types

of thrombotic events with thrombocytopenia and Guillain-Barre syndrome with Ad26.COV2.S. These issues are discussed in detail elsewhere. (See 'BNT162b2 (Pfizer-BioNTech COVID-19 vaccine)' below and 'mRNA-1273 (Moderna COVID-19 vaccine)' below and 'Specific safety concerns' below.)

Uncommon skin reactions have also been reported following vaccination. These are also discussed elsewhere. (See "COVID-19: Cutaneous manifestations and issues related to dermatologic care", section on 'Considerations for vaccination to prevent SARS-CoV-2 infection'.)

Other complications (including more common venous thromboembolic events without thrombocytopenia such as deep vein thrombosis or pulmonary embolism, Bell's palsy, tinnitus) have been reported in vaccine recipients but have **not** been identified as causally related vaccine-associated adverse events. (See 'Immunogenicity, efficacy, and safety of select vaccines' below.)

Definition of "up to date on vaccination" — In the United States, individuals are considered "up to date" on COVID-19 vaccination if they have completed a primary series and received all recommended booster vaccines based on age and comorbidities [123]. Those who have received a primary series but are not yet eligible for the booster vaccine because of age or timing of the last vaccine dose are still considered up to date.

The CDC had also used the term "fully vaccinated" to refer to individuals who had completed the primary COVID-19 vaccine series at least two weeks prior. However, since the introduction of booster vaccines, public health recommendations have evolved to focus on whether individuals are up to date on vaccination as detailed above. The term "fully vaccinated" is probably no longer useful, as vaccination recommendations vary by age and degree of immunocompromise.

For individuals who were vaccinated in another country, the CDC notes that individuals who received a primary series with a vaccine listed for use by the World Health Organization (WHO) do not need to repeat a primary series with vaccines available in the United States. If they are eligible for an initial booster vaccine and have not yet received one, the CDC recommends administration of a booster dose (or two booster doses, depending on their age and comorbidities), at which point they are considered up to date on vaccination. (See 'Role of booster vaccinations' below.)

Post-vaccine public health precautions — Although SARS-CoV-2 infection might still occur despite vaccination, the risk is substantially lower. Recommendations on public health precautions following vaccination have evolved with new developments in the pandemic (eg,

emergence of the highly transmissible Delta and Omicron variants), and the approach should be tailored to the overall rate of transmission in the community. Recommendations on mask-wearing post-exposure management are discussed in detail elsewhere. (See "COVID-19: Epidemiology, virology, and prevention", section on 'Post-exposure management'.)

EUA status of certain vaccines — In addition to standard counseling around vaccine information, vaccine providers are required to inform potential recipients when a vaccine is available under emergency use authorization (EUA). It is not necessary, however, for recipients to sign informed consent documents. (See 'Steps to vaccine availability and delivery' below.)

Contraindications and precautions (including allergies)

- **Contraindications** – The following are the only contraindications to COVID-19 vaccination [42]:

  - A severe allergic reaction (eg, anaphylaxis) to a previous COVID-19 vaccine dose or to a component of the vaccine or a known (diagnosed) allergy to a component of the vaccine.

    Symptoms of immediate reactions are listed on the CDC website. Isolated hives that develop more than four hours after vaccine receipt are unlikely to represent an allergic reaction to the vaccine. (See "COVID-19: Allergic reactions to SARS-CoV-2 vaccines", section on 'Delayed urticarial reactions'.)

    The mRNA vaccines, BNT162b2 (Pfizer-BioNTech COVID-19 vaccine) and mRNA-1273 (Moderna COVID-19 vaccine), each contain polyethylene glycol, and NVX-CoV2373 (Novavax COVID-19 vaccine) and Ad26.COV2.S (Janssen COVID-19 vaccine, also known as the Johnson & Johnson vaccine) each contain polysorbate. Allergic reaction to polysorbate is a contraindication to NVX-CoV2373 and Ad26.COV2.S but a precaution to mRNA vaccines.

  - A history of thrombosis with thrombocytopenia following an Ad26.COV2.S or any other adenoviral vector COVID-19 vaccine is a contraindication to Ad26.COV2.S. Ad26.COV2.S is also not recommended for those with a history of thrombosis or thrombocytopenia that is thought to be immune mediated (including heparin-induced thrombocytopenia) or for those who developed Guillain-Barre syndrome following a prior dose of Ad26.COV2.S.

- **Precautions** – Precautions to a specific COVID-19 vaccine include allergic reactions to other vaccines. Patients with such reactions can generally receive a COVID-19 vaccine but

warrant longer post-vaccination monitoring than usual (see 'Monitoring for immediate reactions to vaccine' below):

- Immediate allergic reaction to any other (non-COVID-19) vaccine or injectable therapy.
- Prior immediate but nonsevere allergic reactions (eg, hives, angioedema that did not affect the airway) to a COVID-19 vaccine is a precaution (not contraindication) to that same vaccine type.
- Allergy-related contraindication to one type of COVID-19 vaccine is a precaution to other types of COVID-19 vaccine because of potential cross-reactive hypersensitivity.

Allergy consultation can be helpful to evaluate suspected allergic reactions to a COVID-19 vaccine or its components and assess the risk of future COVID-19 vaccination. This is discussed in detail elsewhere. (See "COVID-19: Allergic reactions to SARS-CoV-2 vaccines", section on 'Possible anaphylaxis'.)

Caution is also warranted for those with a history of myocarditis or pericarditis following a COVID-19 vaccine, MIS, or Guillain-Barre syndrome. These issues are discussed elsewhere. (See 'Myocarditis' below and 'History of SARS-CoV-2 infection' above and 'Guillain-Barre syndrome' below.)

Caution may be warranted prior to administering any vaccine in certain rare but life-threatening conditions, such as acquired thrombotic thrombocytopenia purpura and capillary leak syndrome, exacerbations of which have been reported following COVID-19 vaccination [124,125]. (See "Immune TTP: Management following recovery from an acute episode and during remission", section on 'Vaccinations' and "Idiopathic systemic capillary leak syndrome", section on 'Prodromal symptoms and triggers'.)

History of thromboembolic disease is not a contraindication to vaccination with mRNA vaccines or NVX-CoV2373. Although very rare cases of unusual types of thrombosis associated with thrombocytopenia have been reported following vaccination with both ChadOx1 nCoV-19/AZD1222 (AstraZeneca COVID-19 vaccine) and Ad26.COV2.S, there has not been a concerning signal for this type of thrombotic complication with mRNA COVID-19 vaccines. Furthermore, there is no evidence that classic risk factors for thrombosis (eg, thrombophilic disorders or prior history of venous thromboembolism not associated with thrombocytopenia) increase the risk for this rare adverse event [126], and individuals with these can receive any approved or authorized COVID-19 vaccine. (See 'Thrombosis with thrombocytopenia' below and "COVID-19: Vaccine-induced immune thrombotic thrombocytopenia (VITT)", section on 'Prevention (common questions)'.)

Other reactions or conditions that are neither precautions nor contraindications include:

- Late local reactions characterized by a well-demarcated area of erythema appearing at the injection site approximately a week after mRNA COVID-19 vaccination have been reported, with recurrence occurring in some individuals after repeat vaccination [127]. This may occur more frequently with mRNA-1273 than with BNT162b2 [128]. This type of reaction is not a contraindication to vaccination, and individuals who experience this after the initial mRNA vaccine dose can proceed with the second dose as scheduled [42]. (See "COVID-19: Allergic reactions to SARS-CoV-2 vaccines", section on 'Late local reactions'.)

- Facial swelling in areas previously injected with cosmetic dermal fillers has also been rarely reported following vaccination with the mRNA COVID-19 vaccines. Dermal fillers are not a contraindication to COVID-19 vaccination, and no specific precautions are recommended [42]. However, it is reasonable to advise individuals with dermal fillers of the possibility of post-vaccination swelling. This is discussed elsewhere. (See "COVID-19: Cutaneous manifestations and issues related to dermatologic care", section on 'Soft tissue fillers'.)

- Anticoagulation is not a contraindication to vaccination; excess bleeding is unlikely with intramuscular vaccines in patients taking anticoagulants [129]. Such patients can be instructed to hold pressure over the injection site to reduce the risk of hematoma. (See "Standard immunizations for nonpregnant adults", section on 'Patients on anticoagulation'.)

Monitoring for immediate reactions to vaccine — All individuals should be monitored for immediate vaccine reactions following receipt of any COVID-19 vaccine.

The following warrant monitoring for 30 minutes:

- Precautions to the administered vaccine (immediate reaction to any vaccine or injectable therapy; contraindication to the other vaccine type) (see 'Contraindications and precautions (including allergies)' above)

- History of anaphylaxis due to any cause

All other individuals are monitored for 15 minutes.

Vaccines should be administered in settings where immediate allergic reactions, should they occur, can be appropriately managed. Recognition and management of anaphylaxis are discussed in detail elsewhere (table 5). (See "Anaphylaxis: Acute diagnosis" and "Anaphylaxis: Emergency treatment".)

Anaphylaxis has been reported following administration of both mRNA COVID-19 vaccines [130]. Following the first several million doses of mRNA COVID-19 vaccines administered in the United States, anaphylaxis was reported at approximate rates of 4.5 events per million doses [131-133]. The vast majority of these events occurred in individuals with a history of allergic reactions and occurred within 30 minutes. The mechanism for the anaphylaxis is under investigation and has not been determined. Some suggest that it is IgE mediated, with polyethylene glycol as the inciting antigen. However, other complement-mediated mechanisms have been suggested in individuals without a previous history of allergy. Evaluation of patients with possible anaphylaxis following COVID-19 vaccination is discussed elsewhere. (See "COVID-19: Allergic reactions to SARS-CoV-2 vaccines", section on 'Possible anaphylaxis'.)

Reporting of adverse events — To facilitate ongoing safety evaluation, vaccine providers are responsible for reporting vaccine administration errors, serious adverse events associated with vaccination, cases of multisystem inflammatory syndrome (MIS), and cases of COVID-19 that result in hospitalization or death through the Vaccine Adverse Event Reporting System (VAERS). (See 'Ongoing safety assessment' below.)

Details on the efficacy and safety of available COVID-19 vaccines are discussed elsewhere. (See 'Immunogenicity, efficacy, and safety of select vaccines' below.)

APPROACH TO VACCINATION IN OTHER COUNTRIES

Various vaccines are available in different countries. A list of vaccines that have been authorized in at least one country can be found at covid19.trackvaccines.org/vaccines. Data on some of these vaccines can be found elsewhere. (See 'Immunogenicity, efficacy, and safety of select vaccines' below.)

Dosing schedules vary by vaccine. Additionally, different countries may have specific recommendations for vaccine use. Clinicians should refer to local guidelines for vaccine recommendations in their location. (See 'Society guideline links' below.)

Several countries had paused use of ChAdOx1 nCoV-19/AZD1222 to investigate scattered reports of thromboembolic events; many have since resumed use, in some cases with age restrictions. This is discussed in detail elsewhere. (See 'Thrombosis with thrombocytopenia' below.)

IMMUNOGENICITY, EFFICACY, AND SAFETY OF SELECT VACCINES

Selected vaccines that are available for use in different countries are described here (table 2). They represent different vaccine approaches, including RNA vaccines, replication-incompetent vector vaccines, recombinant protein vaccines, and inactivated vaccines; the general features of these different platforms are described elsewhere. (See 'General principles' above.)

Immunogenicity, efficacy, and safety of specific vaccines are discussed below. General issues related to breakthrough infections, impact on transmission, effectiveness against variants of concern, and duration of effect are discussed elsewhere. (See 'Ongoing safety assessment' below.)

BNT162b2 (Pfizer-BioNTech COVID-19 vaccine) — This mRNA vaccine is delivered in a lipid nanoparticle to express a full-length spike protein (table 2). Clinical use of the vaccine is discussed elsewhere. (See 'Approach to vaccination in the United States' above.)

- **Efficacy and immunogenicity** – Randomized trials in children and adults demonstrate a substantially reduced risk of symptomatic and severe COVID-19 in the first several months after BNT162b2 vaccination. In large placebo-controlled trials, vaccine efficacy of the two-dose primary series in preventing symptomatic COVID-19 at a median of two-month follow-up was 95 percent (95% CI 90.3-97.6) for individuals aged 16 years or older [134,135], 100 percent (95% CI 75.3-100) for individuals aged 12 to 15 years [136], and 91 percent for individuals aged 5 to 11 years [137]. Among adults ≥65 years of age who had other medical comorbidities or obesity, vaccine efficacy was 91.7 percent (95% CI 44.2-99.8). On longer follow-up, vaccine efficacy remained high but slightly decreased to 90 percent at two to four months post-vaccination and 84 percent at four to six months [138]. Of 30 severe infections (ie, with hypoxia, organ dysfunction, or critical illness) among nearly 50,000 trial participants over six months, only 1 occurred in a vaccinated individual. In a small trial of children aged six months to four years, vaccine efficacy was 80.4 percent (95% CI 14.1-96.7), although the estimate was uncertain because of the low number of cases overall [108]. Two participants were seen in the emergency department or hospitalized with COVID-19; both were vaccine recipients who also had coinfection with other respiratory viruses.

  Observational data from various countries following their national roll-outs of BNT162b2 support the trial findings in adults and adolescents [16-19,139-151]. Specifically, BNT162b2 has been associated with approximately 90 percent or higher vaccine effectiveness in preventing COVID-19-related hospitalization, intensive care unit admissions, and death among adolescents and adults. Some, but not all observational data suggest that vaccine effectiveness in children aged 5 through 11 years may be lower than that among older adolescents, but it is unclear how much of that difference is related to reduced vaccine

effectiveness in general against the Omicron variant, which dominated soon after introduction of vaccine for the younger children; vaccination still substantially reduces COVID-19-associated hospitalizations in this age group, even in the context of Omicron prevalence [152-161].

Vaccine effectiveness wanes over time and may be decreased in protecting against infection with certain SARS-CoV-2 variants, although protection against severe disease due to variants remains substantial. These issues are discussed in detail elsewhere. (See 'Waning effectiveness over time and with variants of concern' below.)

These efficacy data are consistent with evidence from immunogenicity studies that demonstrated robust binding and neutralizing antibody responses with BNT162b2, with some variability by age [136,137,162]. Responses in participants ≥65 years old were generally lower than in younger subjects, but still comparable or higher than titers in convalescent plasma. For children under five years old, three doses (of a lower vaccine dose) were necessary to elicit neutralizing antibody levels comparable to those in older individuals after two doses [108].

Neutralizing antibody titers decline with time following BNT162b2 vaccination in adults; in one study, steeper declines in neutralizing titers over six months were observed among males, individuals ≥65 years old, and immunocompromised individuals [163]. Neutralizing activity is lower against the Delta variant (B.1.617.2) [164-166] and substantially lower against the Omicron variant (B.1.1.529) compared with activity against previously circulating strains.

Preliminary data presented in a press release from the manufacturer indicated that in children aged six months to five years, three doses of a low-dose BNT162b2 formulation resulted in antibody responses similar to those seen in young adults following two standard doses [167]. Additional details are pending.

- **Common side effects** – Local and systemic adverse effects are relatively common, particularly after the second dose; most are of mild or moderate severity (ie, do not prevent daily activities) and are limited to the first two days after vaccination [119,133,134]. Injection site reactions (mainly pain, but also redness, swelling, and pruritus) occur in approximately 65 percent; fatigue, headache, and myalgias in approximately 40 to 50 percent; and fevers, chills, and joint pain in approximately 20 percent [119]. Rates are slightly higher among adolescents aged 12 through 15 years and slightly lower among children aged 5 through 11 years [136,137]. Among young children, irritability, crying, drowsiness, and loss of appetite were common; febrile seizures were

rare [108]. Local and systemic reactions occur less frequently among recipients aged 65 years or older but are still relatively common.

- **Serious adverse effects** – Myocarditis and pericarditis, mainly in male adolescents and young adults, have been reported more frequently than expected following receipt of BNT162b2. This is discussed in detail elsewhere. (See 'Myocarditis' below.)

  Anaphylaxis following vaccination has been reported at an approximate rate of 5 events per 1 million doses; 80 percent of anaphylaxis cases have occurred in individuals with a history of allergic reactions and 90 percent occurred within 30 minutes [131]. Other reported allergic reactions included pruritus, rash, scratchy sensations in the throat, and mild respiratory symptoms [168]. (See "COVID-19: Allergic reactions to SARS-CoV-2 vaccines", section on 'mRNA vaccines'.)

  Other major adverse events have not been consistently associated with BNT162b2 receipt [169]. Rare cases of Bell's palsy were noted in the phase III trial in adults (four in vaccine and zero in placebo recipients) [134]; however, the rate did not exceed background rates found in the general population (15 to 30 cases per 100,000 people per year), and post-vaccine monitoring has not identified an association between vaccination and Bell's palsy [131]. In a large cohort study from Israel, BNT162b2 receipt was most strongly associated with myocarditis, lymphadenopathy, appendicitis, and herpes zoster [170].

mRNA-1273 (Moderna COVID-19 vaccine) — This messenger RNA (mRNA) vaccine was one of the first vaccines for SARS-CoV-2 to be produced; it was developed and administered to humans within two months of publication of the SARS-CoV-2 genomic sequence. The vaccine utilizes mRNA delivered in a lipid nanoparticle to express a full-length spike protein (table 2). Clinical use of the vaccine is discussed elsewhere. (See 'Approach to vaccination in the United States' above.)

- **Efficacy and immunogenicity** – Randomized trials in adults demonstrate a substantially reduced risk of symptomatic and severe COVID-19 in the first several months after mRNA-1273 vaccination. In a large placebo-controlled trial, vaccine efficacy of the two-dose primary series in preventing symptomatic COVID-19 at a median of two-month follow-up was 94.1 percent (95% CI 89.3-96.8) among adults 18 years or older [171]. Among adults ≥65 years of age, vaccine efficacy was 86.4 percent (95% CI 61.4-95.5). After a median follow-up of 5.2 months, vaccine efficacy was 93.2 percent for symptomatic infection (9.6 versus 136.6 cases per 100 person-years with placebo) and 98.2 percent for severe disease (ie, with hypoxia, organ dysfunction, or critical illness; 2 versus 106 cases with placebo) [172]. Limited trial data also suggest that vaccine efficacy against symptomatic COVID-19

is high in children aged 12 to 17 years (100 percent, 95% CI 28.9-nonevaluable) and aged 6 to 11 years (69 percent, 95% CI -131.4-95.8), although the estimates of effect were uncertain because of the low number of cases [107]. Efficacy was lower (41.5 percent, 95% CI 23.8-55) in a trial of younger children that was performed when Omicron variant was circulating, although this estimate is largely consistent with observational data on vaccine effectiveness against Omicron in adults. There were no severe COVID-19 cases in any of the trials of children.

Observational data evaluating vaccine effectiveness also support the trial findings in adults [16,147,148,150,173-175]. Specifically, mRNA-1273 has been associated with approximately 90 percent or higher vaccine effectiveness in preventing COVID-19-related emergency visits, hospitalization, intensive care unit admission, and death.

Vaccine effectiveness wanes over time and may be decreased in protecting against infection with certain SARS-CoV-2 variants, although protection against severe disease due to variants remains substantial. These issues are discussed in detail elsewhere. (See 'Waning effectiveness over time and with variants of concern' below.)

These efficacy data are consistent with evidence from immunogenicity studies that demonstrated robust binding and neutralizing antibody responses with mRNA-1273 in adults of all ages [176,177]. Immunogenicity in children or adolescents aged 6 months to 5 years (with a quarter-dose), aged 6 to 11 years (with a half-dose), and aged 12 to 17 years (with a standard dose) is comparable to or higher than that seen in young adults [178-180]. Over six months, antibody titers decline slightly but remain high and neutralizing activity persists [181]. Vaccination with mRNA-1273 is associated with higher antibody titers after the second dose compared with BNT162b2 [182,183]. Neutralizing activity is lower against Delta (B.1.617.2) [165] and substantially lower against Omicron (B.1.1.529) compared with activity against previously circulating strains.

- **Common side effects** – Local and systemic adverse effects are relatively common, particularly after the second dose; most are of mild or moderate severity (ie, do not prevent daily activities or require pain relievers) and are limited to the first two days after vaccination [119,133,184]. Injection site reactions (mainly pain, but also redness, swelling, and pruritus) occur in approximately 75 to 80 percent; fatigue, headache, and myalgias in approximately 50 to 60 percent; and fevers, chills, and joint pain in approximately 30 to 40 percent [119]. Local and systemic reactions occur less frequently among recipients 65 years or older but were still relatively common. Among young children, irritability, crying, sleepiness, and loss of appetite were common; febrile seizures were rare [107].

- **Severe adverse effects** – Myocarditis and pericarditis, mainly in male adolescents and young adults, have been reported more frequently than expected following receipt of mRNA-1273. This is discussed in detail elsewhere. (See 'Myocarditis' below.)

  Anaphylaxis following vaccination has been reported at an approximate rate of 2.8 events per 1 million doses; 86 percent of anaphylaxis cases have occurred in individuals with a history of allergic reactions, and 90 percent occurred within 30 minutes [131,168]. (See "COVID-19: Allergic reactions to SARS-CoV-2 vaccines", section on 'mRNA vaccines'.)

  In trials among adults, there were rare cases of Bell's palsy that were considered potentially related to vaccination (three in the vaccine and one in the placebo group). However, the rate did not exceed the background rate in the general population (15 to 30 cases per 100,000 people per year), and post-vaccine monitoring has not identified an association between vaccination and Bell's palsy [131].

  No other major vaccine-associated adverse events have been identified in post-vaccine surveillance [169].

NVX-CoV2373 (Novavax COVID-19 vaccine) — This is a recombinant protein subunit vaccine composed of trimeric spike glycoproteins and a potent Matrix-M1 adjuvant (table 2). Clinical use of the vaccine is discussed elsewhere. (See 'Approach to vaccination in the United States' above.)

- **Efficacy and immunogenicity** – In a phase III efficacy trial in the United States and Mexico, NVX-CoV2373 had 90.4 percent (95% CI 82.9-94.6) efficacy in preventing symptomatic COVID-19 in seronegative individuals aged 18 to 84 years [185]. The four severe cases occurred in the placebo group. Among participants 65 year of age or older, the estimate of vaccine efficacy was lower, but was also less certain because of the small number of cases in this subgroup (78.6 percent, 95% CI -16.64 to 96). Similar vaccine efficacy (89.7 percent, 95% CI 80.2-94.6) was reported in a phase III trial in the United Kingdom [186].

- **Safety and side effects** – Local and systemic adverse effects are relatively common, particularly after the second dose, with a median time to onset of two days and median durations of two to three days; most are of mild or moderate severity (ie, do not prevent undertaking daily activities or require pain relievers). The most common systemic reactions were fatigue/malaise, headache, and myalgias. Systemic reactions were more common among recipients under 65 years of age.

In the phase III efficacy trial, serious adverse event rates in the vaccine and placebo group were similar [185,187]. However, there were six cases of myocarditis/pericarditis in the vaccine group, five of which occurred within two weeks of vaccine receipt, and four of which occurred in young males, consistent with the pattern of myocarditis associated with mRNA vaccines (see 'Myocarditis' below). There were also small numerical excesses of certain rare adverse events in the vaccine groups (including uveitis, thromboembolic events, cholecystitis, and cardiomyopathy), but the limited data cannot establish or rule out a causal relationship.

Ad26.COV2.S (Janssen/Johnson & Johnson COVID-19 vaccine) — This vaccine is based on a replication-incompetent adenovirus 26 vector that encodes a stabilized spike protein (table 2). Clinical use of the vaccine is discussed elsewhere. (See 'Approach to vaccination in the United States' above.)

- **Efficacy and immunogenicity** – Randomized trials in adults demonstrate a substantially reduced risk of symptomatic and severe COVID-19 in the first several months after Ad26.COV2.S vaccination. In a large placebo-controlled trial, vaccine efficacy of the one-dose primary series in preventing moderate to severe/critical COVID-19 (which included patients with pneumonia, dyspnea, tachypnea, or at least two symptoms of COVID-19) at a median of two-month follow-up was 66.9 percent efficacy (95% CI 59.0-73.4) in adults age 18 years or older [188]. Vaccine efficacy against severe/critical infection (ie, with hypoxia, organ dysfunction, or critical illness) trended higher at 78 and 85 percent after 14 and 28 days post-vaccination. Efficacy estimates after a median of four months follow-up were 56.3 percent (95% CI 51.3-60.8) for at least moderate COVID-19 and 74.6 percent (95% CI 64.1-82.1) for severe/critical COVID-19 [189].

  Observational data evaluating vaccine effectiveness largely support the trial findings; a single dose of Ad26.COV2.S has been associated with vaccine effectiveness of 67 to 75 percent against COVID-19-related emergency care and hospitalization and 83 percent against COVID-19-related death [16,190,191]. These efficacy data are consistent with evidence from immunogenicity studies that demonstrated post-vaccination binding and neutralizing antibody responses that overlapped with but were slightly lower than those in convalescent plasma [192,193]. These neutralizing responses are largely stable over eight months with both one- and two-dose regimens [194], in contrast to the neutralizing antibody levels following mRNA vaccination, which wane over time (although remain higher than after Ad26.COV2.S) [195]. Neutralizing activity is also retained against the Delta (B.1.617.2) variant at only a slightly lower level than against previously circulating strains but is substantially reduced against Omicron (B.1.1.529).

Waning vaccine effectiveness and impact of SARS-CoV-2 variants are discussed in detail elsewhere. (See 'Waning effectiveness over time and with variants of concern' below.)

- **Safety and side effects** – Local and systemic adverse effects are relatively common; most are of mild or moderate severity (ie, do not prevent undertaking daily activities or require pain relievers) and most commonly occur the first day after vaccination [196]. Among over 330,000 vaccine recipients in the United States who responded to post-vaccination surveys, 76 percent reported at least one systemic reaction and 61 percent at least one injection site reaction in the first week. The most common systemic reactions were fatigue, pain, and headache. Anxiety-related events, including tachycardia, hyperventilation, light-headedness, and syncope, have also been reported following Ad26.COV2.S administration [197].

  In the phase III efficacy trial, serious adverse event rates in the vaccine and placebo group were similar [188]. There were more cases of thromboembolic events (11 versus 3), tinnitus (6 versus 0), and seizures (4 versus 1) among vaccine compared with placebo recipients, but the numbers of events were too few to determine whether there is a causal association with vaccination. In a report of over 400,000 health care workers who received Ad26.COV2.S in South Africa, there were two cases of thrombosis with thrombocytopenia and four cases of Guillain-Barre syndrome following vaccination; the incidence of these did not exceed the expected incidence in the general population [198]. However, other studies suggest that the vaccine is associated with a specific syndrome of thrombosis with thrombocytopenia and is possibly associated with Guillain-Barre syndrome; these are discussed in detail elsewhere. (See 'Thrombosis with thrombocytopenia' below and 'Guillain-Barre syndrome' below.)

ChAdOx1 nCoV-19/AZD1222 (University of Oxford, AstraZeneca, and the Serum Institute of India) — This vaccine is based on a replication-incompetent chimpanzee adenovirus vector that expresses the spike protein. It is given intramuscularly as two doses. The World Health Organization (WHO) recommends that the two doses be given 8 to 12 weeks apart [199].

- **Efficacy and immunogenicity** – Randomized trials in adults demonstrate a substantially reduced risk of symptomatic COVID-19 in the first several months after vaccination. In large placebo-controlled trials, vaccine efficacy of a two-dose primary series in preventing symptomatic COVID-19 at a median of two-month follow-up was 70 to 76 percent (95% CI 54.8-80.6) at or after 14 days following the second dose [200,201]. Additional analysis of this trial suggested that receipt of the second dose at 12 weeks or later was associated with higher vaccine efficacy than receipt at <6 weeks (81 versus 55 percent) [202]. These

findings lend support to extending the time interval between the first and second dose to 12 weeks.

Observational data from various countries following their national roll-outs of ChAdOx1 nCoV-19/AZD1222 also support the trial findings [18,203], although they suggest that effectiveness, even against severe infection, wanes over time [204]. Waning vaccine effectiveness and impact of SARS-CoV-2 variants are discussed in detail elsewhere. (See 'Waning effectiveness over time and with variants of concern' below.)

These efficacy data are consistent with evidence from immunogenicity studies that demonstrated robust binding and neutralizing antibody responses in vaccine recipients [205-207]. The Delta (B.1.617.2) and Omicron (B.1.1.529) variants evade immune responses in some vaccinated individuals [166,208].

- **Safety and side effects** – In earlier-phase trials, fatigue, headache, and fever were relatively common after vaccine receipt and were severe in up to 8 percent of recipients [205]. In the phase III trial, there were two cases of transverse myelitis in ChAdOx1 nCoV-19 vaccine recipients [200]. One was thought to be possibly related to vaccination and was described as an idiopathic, short-segment spinal cord demyelination; the other was in a participant with previously unrecognized multiple sclerosis and thought to be unrelated to the vaccine. The vaccine also may be associated with an extremely small risk of thrombotic events associated with thrombocytopenia, which is discussed in detail elsewhere. (See 'Thrombosis with thrombocytopenia' below.)

  The general thromboembolic risk with ChadOx1 nCoV-19/AZD1222 is uncertain. Some analyses have suggested that the total rate of thromboembolic events following vaccination is lower than that expected based on the background rate in the general population [209,210]. However, separate analyses from Europe suggest a slightly higher total rate of thromboembolic events (including pulmonary embolism) following ChadOx1 nCoV-19/AZD1222 than expected [211,212].

Other vaccines — Details on select vaccines that are available internationally are presented below. A list of vaccines that have been authorized in at least one country can be found at covid19.trackvaccines.org/vaccines.

- **Convidencia (CanSino Biologics)** – This vaccine is based on a replication-incompetent adenovirus 5 vector that expresses the spike protein. It is given as a single intramuscular dose. In early clinical trials, both pre-existing immunity to adenovirus 5 and older age were associated with lower titers of binding and neutralizing antibodies following vaccination; this may limit its utility in locations where pre-existing immunity is prevalent

[213]. In a randomized phase III trial, vaccine efficacy was 57.5 percent (95% CI 39.7-70.0) for symptomatic infection and 91.7 percent (95% CI 36.1-99.0) for severe disease [214]. This vaccine is available in China and some other countries, including Mexico and Pakistan.

- **Gam-COVID-Vac/Sputnik V (Gamaleya Institute)** – This is a vaccine developed in Russia that uses two replication-incompetent adenovirus vectors that express a full-length spike glycoprotein (table 2). The vaccine is given intramuscularly as an initial adenovirus 26 vector dose followed by an adenovirus 5 vector boosting dose 21 days to 3 months later [215]. This vaccine is available in Russia and several other countries, including Mexico. According to interim analysis of a phase III trial, this vaccine had 91.6 percent (95% CI 85.6-95.2) efficacy in preventing symptomatic COVID-19 at the time of the second dose [216]. All 20 cases of severe COVID-19 that occurred 21 days after the first dose were in the placebo group. Local and systemic flu-like reactions were more common in the vaccine group, at rates of 15 and 5 percent, respectively. No serious adverse events were deemed related to vaccine.

- **Covilo/BBIBP-CorV (Sinopharm)** – This is an inactivated, whole-virus vaccine with an aluminum hydroxide adjuvant. It is given intramuscularly in two doses 28 days apart. In a phase III efficacy trial, vaccine efficacy was estimated as 78 percent (95% CI 65-86) compared with an alum-only placebo [217]. Only two severe cases occurred, both in the placebo group. Systemic and injection site reactions occurred at similar frequencies with vaccine or placebo (eg, pain in 20 to 27 percent, headache in 13 percent, fatigue in 11 percent). This vaccine is available in China and some other countries, including the United Arab Emirates and Hungary.

- **CoronaVac (Sinovac)** – This inactivated COVID-19 vaccine was developed in China; it has an aluminum hydroxide adjuvant. The vaccine is given intramuscularly in two doses 28 days apart. According to interim results of a phase III trial in Turkey, vaccine efficacy was 83.5 percent (95% CI 65.4–92.1) [218]; however, lower efficacy rates have been reported in small trials from different countries [219,220]. In an observational study that included over 10 million individuals in Chile, estimated vaccine effectiveness was 70 percent for preventing COVID-19 and 86 to 88 percent for preventing hospital admission or death [221]; a subsequent study in Brazil reported lower vaccine effectiveness among adults older than 70 years in the context of prevalent Gamma variant (47, 56, and 61 percent against COVID-19, hospitalization, and death, respectively) [222]. This vaccine is available in China and some other countries, including Brazil, Chile, Indonesia, Mexico, and Turkey.

- **Covaxin (Bharat Biotech/Indian Council of Medical Research)** – This inactivated COVID-19 vaccine (also called BBV152) was developed and is being used in India; it has an aluminum hydroxide and a toll-like receptor agonist adjuvant. It is given intramuscularly in two doses 29 days apart. In a randomized trial, vaccine efficacy against symptomatic COVID-19 was 78 percent (95% CI 65-86); there was 1 case of severe COVID-19 in the vaccine group and 15 in the placebo group [223]. Serious adverse events were not deemed related to vaccine except for one possibly related case of immune thrombocytopenic purpura.

- **ZyCoV-D (Zydus Cadila)** – This is the first DNA COVID-19 vaccine made available, first authorized in India in August 2021 [224]. A needleless device delivers the vaccine subcutaneously with a high-pressure stream. In a trial of 28,000 participants aged 12 years or older, vaccine efficacy against symptomatic COVID-19 was 67 percent (95% CI 47.6-80.7) following three doses, each given 28 days apart; only one severe case of COVID-19, in the placebo group, occurred [225].

GENERAL EFFICACY ISSUES

Role of booster vaccinations

Waning effectiveness over time and with variants of concern — Although the initial clinical trials reported extremely high efficacy rates of COVID-19 vaccines (in particular with mRNA vaccines) in preventing laboratory-confirmed symptomatic infection, their observed effectiveness against infection has decreased over time because of waning immunity and immune evasion by certain circulating SARS-CoV-2 variants. Decreases in observed vaccine effectiveness may also be related to overall decreases in the risk of severe infection because of a higher prevalence of prior infection (which also provides protection against severe infection) as well as variants associated with milder infection. Although vaccine effectiveness against severe disease has also decreased over time and in the setting of Omicron subvariants, COVID-19 vaccines continue to provide good levels of protection against severe disease; the risk of hospitalization and death associated with COVID-19 has consistently remained higher among unvaccinated individuals [23,24].

- **Waning effectiveness** – Multiple observational studies have suggested that vaccine protection against SARS-CoV-2 infection wanes over time (after both primary series and booster vaccinations) in children and adults [33,226-235]. Protection against hospitalization and death also wanes somewhat, but less than protection against infection [236-243].

As an example, in a study of statewide data in North Carolina that included over 10 million adults, adjusted mRNA vaccine effectiveness at seven months following the primary series was 54 to 70 percent against infection, 86 to 90 percent against hospitalization, and 90 to 93 percent against death [241]. At 12 months, the same measures were 38 to 47 percent, 60 to 65 percent, and 70 to 75 percent. Similarly, vaccine effectiveness of an mRNA booster dose compared with the primary series peaked at about one month and waned over four to six months, but the booster dose continued to be associated with protection against hospitalization and death. Another study suggested that a primary series and booster dose were associated with a 60 percent reduction in risk of hospitalization at five months [243].

- **Attenuated effectiveness against certain variants of concern** – Several SARS-CoV-2 variants that are concerning for their potential for immune escape have emerged over the course of the pandemic (table 6). For the Omicron variant and its sublineages (BA.1, BA.2, BA.2.12.1, BA.4, and BA.5), COVID-19 vaccines remain effective in preventing severe disease, but effectiveness in preventing symptomatic infection is attenuated.

  Observational studies consistently suggest that vaccination has substantially reduced effectiveness against symptomatic infection with Omicron subvariants compared with other variants and wanes after several months. Effectiveness against severe disease (as reflected by hospitalization) has remained relatively high, particularly among those who received a booster dose. However, effectiveness against severe infection is lower with Omicron than with other variants and also wanes [244-253]. As an example, in an observational study from the United States, vaccine effectiveness against hospitalization within five months of receiving the last of three mRNA COVID-19 vaccine doses was 79 and 60 percent during the BA.1/BA.2 and BA.4/BA.5 periods, respectively, but decreased to 41 and 29 percent more than five months after vaccination [253].

  Consistent with the observed attenuated vaccine effectiveness against infection with the Omicron subvariant, neutralizing activity of sera from vaccinated individuals is reduced against Omicron compared with the original Wuhan strain virus and the Delta variant; the majority of infection-naïve individuals who received a primary vaccine series have no detectable neutralizing activity against Omicron [254-263]. However, previously infected individuals who received a primary series and individuals who receive booster vaccination retain adequate neutralizing titers against Omicron sublineages BA.1 and BA.2; neutralizing titers from such individuals are usually lower for BA.4 and BA.5 but in most cases still above baseline [264-267]. The discrepancy between the lack of neutralizing activity against Omicron in sera from vaccinated individuals and the persistence of

protection against severe disease with vaccination may be in part because neutralizing activity is not the only immune measure of vaccine protection. Vaccine- or infection-induced cellular immunity appears robust against Omicron [268-271]. (See "COVID-19: Epidemiology, virology, and prevention", section on 'Omicron (B.1.1.529) and its sublineages'.)

Monovalent booster effectiveness and safety — Because of waning immunity and decreased vaccine efficacy against circulating variants, public health authorities in many countries have recommended booster vaccines after the primary series [272]. In the United States, monovalent mRNA vaccine booster doses are no longer recommended. The bivalent mRNA vaccines are recommended for booster doses. This is discussed elsewhere. (See 'Bivalent mRNA vaccine booster effectiveness and immunogenicity' below.)

- **Effectiveness of a single monovalent booster dose** – A booster vaccine improves vaccine effectiveness in the short term, including in the context of Omicron prevalence [273-282]. In a placebo-controlled, randomized trial of 10,000 individuals who had received two primary series doses of BNT162b2, vaccine efficacy of a third booster dose (given a median of 11 months after the prior dose) against symptomatic COVID-19 was 95.3 percent (95% CI 89.5-98.3) in the first two months [273]. Only two severe COVID-19 cases occurred, both in the placebo group, and neither patient was hospitalized. Similarly, in an observational study from Israel of over four million individuals aged 16 years or older who had received two doses of BNT162b2 at least five months previously, receipt of a booster dose was associated with a 10-times lower rate of infection in all age groups compared with those who did not receive a booster (adjusted rate difference of 57 to 90 infections per 100,000 days, depending on age group) and among individuals 60 years or older, an 18-times lower rate of severe illness (absolute difference 5.4 cases per 100,000 days) [274]. Observational data suggest that a booster dose is associated with enhanced short-term vaccine effectiveness in individuals 12 to 16 years of age [151,156]. Data on booster doses in children aged 5 to 11 years are limited to an unpublished trial demonstrating a sharp increase in neutralizing activity following a third BNT162b2 dose [283].

  Data informing the use of heterologous booster vaccines are discussed elsewhere. (See 'Mixing vaccine types' above.)

- **Effectiveness of a second monovalent booster dose** – An additional booster dose appears to improve relative vaccine effectiveness against both infection and severe disease, at least in the short term [284-289]. In a retrospective study from Israel that included over 1 million individuals ≥60 years old who had received a primary series and an initial booster dose with BNT162b2, receipt of a second booster dose at least four months

after the last was associated with twofold lower risk of confirmed infection and a 3.5-fold lower risk of severe infection [284]. The risk reduction for confirmed infection waned by eight weeks after the second booster dose, whereas the risk reduction for severe infection remained stable over the study period. Another study from Israel similarly suggested that a second booster dose was associated with a reduction in COVID-19-related death (adjusted hazard ratio 0.22) [285]. However, in both studies, the overall risk of severe disease or death was very low regardless of second booster, the follow-up period was very short (only 40 to 60 days), and the study design could not exclude the possibility that other differences between the two groups (eg, behavior, health status) could have contributed to the findings.

Limited evidence suggests that the added protection of a second booster dose against infection wanes after several months [290].

- **Safety of booster doses** – The rate and severity of adverse reactions following booster doses are similar to those reported following a primary series. For mRNA vaccines, local and systemic reactions are reported slightly less frequently after the booster dose than the second dose and less frequently after the second booster dose than the first [291,292]. The risk of myocarditis also appears lower after a booster dose than the second dose of an mRNA vaccine [291,293,294]. Following 82.6 million booster doses administered to adults in the United States, there were 37 reports to the Centers for Disease Control and Prevention (CDC) that met criteria for myocarditis [291]. The highest rate was among males aged 18 to 24 years following an mRNA-1273 boost (8.7 per 1 million doses), considerably lower than that reported after the primary series. Similarly, following 2.8 million BNT162b2 booster doses administered to adolescents in the United States, the estimated rate of myocarditis among males aged 12 to 17 years was 11.4 per 1 million booster doses [295]. Analysis of a different, active surveillance system in the United States reported a rate of 188 cases of myocarditis per 1 million booster doses (95% CI 86 to 357 per 1 million doses) among males aged 16 to 17 years, although there was substantial uncertainty around this estimate [296]. (See 'Myocarditis' below.)

Bivalent mRNA vaccine booster effectiveness and immunogenicity — To address issues of both waning efficacy since the last vaccine dose and the attenuated efficacy of COVID-19 vaccines against variants that escape the immune response directed against spike proteins targeted by the original vaccines, some countries have introduced bivalent mRNA COVID-19 vaccine boosters that encode spike protein from the original SARS-CoV-2 strain and from the Omicron variants. In some countries, the Omicron spike protein encoded in the bivalent mRNA COVID-19 vaccines is based on the BA.1 subvariant; in the United States, it is based on the BA.4

and BA.5 subvariants (they have identical spike proteins). Recommendations on bivalent vaccine booster doses in the United States are discussed elsewhere. (See 'Booster dose' above.)

Evidence for the effectiveness of bivalent booster vaccines is limited to observational data but suggests modest to moderate protection against infection depending on time since the last vaccine dose [297-299]. In a study in the United States of over 250,000 symptomatic individuals who were tested for SARS-CoV-2 and had received two to four doses of monovalent vaccines, estimated vaccine effectiveness of an additional bivalent booster dose was 28 to 31 percent among those who had last been vaccinated two to three months previously and 43 to 56 percent among those last vaccinated more than eight months previously [297]. In another study of individuals older than 65 years who had received two to four doses of a monovalent mRNA vaccine at least two months prior, receipt of a bivalent booster dose was associated with 73 percent vaccine effectiveness against COVID-19-associated hospitalization compared with no additional vaccination [298].

Data from immunogenicity studies evaluating bivalent vaccines are mixed and some have not yet been peer reviewed. Some studies, including those performed by the vaccine manufacturers, suggest that bivalent boosters that include the BA.4/5 spike protein induce higher antibody levels against BA.4/5 virus compared with pre-booster levels and compared with monovalent boosters [300-302]. Some of these studies also suggest that the antibody response elicited by the bivalent boosters sufficiently neutralizes other Omicron subvariants, such as BQ.1.1 (table 6). However, in other studies, the antibody response to the bivalent booster was similar to that with the monovalent booster and had minimal neutralizing activity against other Omicron subvariants [303,304]. The reasons for these discrepancies are uncertain but may be related to the specific assay or techniques used. Ultimately, more clinical evidence is needed to better assess the effect of the bivalent vaccines.

Nevertheless, indirect evidence from monovalent booster studies support the use of bivalent vaccines and supports the concept that their effectiveness would be expected to be greater than the monovalent product (see 'Monovalent booster effectiveness and safety' above). Using a bivalent versus monovalent vaccine is analogous to updating the seasonal influenza vaccine; new vaccines are produced each year so that the antigenic targets match circulating virus, and these vaccines are made available globally prior to repeated clinical evaluation because of extensive experience with prior versions.

Booster doses following a primary vaccine series are a distinct issue from administering an additional dose in the primary series (eg, three doses of a primary mRNA vaccine series) for certain immunocompromised patients. Booster doses are also recommended in

immunocompromised individuals who received an additional vaccine dose in the primary series [42]. This is discussed in detail elsewhere. (See 'Immunocompromised individuals' above.)

Breakthrough infections after vaccination — The risk of breakthrough infection is higher with certain variants, such as Delta and Omicron. Nevertheless, the individual risk of severe breakthrough infection with Omicron, particularly among those who received a booster vaccine dose, remains low. (See 'Waning effectiveness over time and with variants of concern' above.)

Breakthrough infection after vaccination is substantially less likely to cause severe disease than infection in unvaccinated individuals [305-308]. In a study of over 1 million vaccinated members of a large health system in the United States, the rates of severe disease and death due to breakthrough COVID-19 were 1.5 and 0.3 per 10,000, respectively [309]. Risk factors for poor outcomes are similar to those for unvaccinated individuals: older age (>65 years) and multiple comorbidities [309,310].

Other observational data suggest that breakthrough infection is associated with a lower number of symptoms, shorter duration of symptoms, lower likelihood of persistent symptoms for >28 days, and a higher likelihood of asymptomatic infection compared with infection in unvaccinated individuals [74,311-313].

Impact on transmission risk — Widespread vaccination reduces the overall transmission risk since vaccinated individuals are less likely to become infected. Data accumulated prior to the emergence of the Omicron variant also suggested that individuals who developed infection despite vaccination may be less likely to transmit to others [314-319].

Vaccination may reduce the likelihood of transmission in the setting of Omicron infection. In a study of individuals in a state prison system in the United States conducted when BA.1 and BA.2 Omicron subvariants were dominant, the overall secondary attack rate from 1126 index SARS-CoV-2 cases to their cellmates was 30 percent [320]. The risk of transmission from index cases who had been vaccinated was compared with index cases who had neither vaccination nor previous infection (22 percent lower in those with vaccination without prior infection and 40 percent lower in those with both vaccination and prior infection). The risk of transmission from vaccinated individuals was lower following booster vaccination than primary series alone. Prior infection alone was also associated with a lower transmission risk.

Immune correlates of protection — Although data remain limited, analyses of vaccine trials support the concept that binding and neutralizing antibody levels against the spike protein and its receptor-binding domain are the primary immune predictors of protection against symptomatic infection, with increasing levels associated with progressively higher vaccine efficacy [321,322]. Data from these studies can help assess likely efficacy of new vaccines or

regimens in different patient populations when large efficacy trials cannot be performed. However, the application to clinical care is uncertain; it is unknown how well results from the various commercially available serologic tests correspond to the measurement of antibody levels in these studies. Furthermore, the immune correlates of protection against severe infection have not been fully elucidated.

SPECIFIC SAFETY CONCERNS

COVID-19 vaccines are exceedingly safe. The primary safety concerns are a very rare risk of myocarditis with mRNA vaccines and very rare risks of thrombosis with thrombocytopenia and possibly Guillain-Barre syndrome with adenoviral vector vaccines. Although myriad adverse events have been reported in individuals following vaccine administration, no other severe events have been clearly associated with vaccination after hundreds of millions of doses administered.

As an example, many patients of child-bearing potential are concerned that COVID-19 vaccination could adversely impact fertility because of specious reports on social media. However, in epidemiologic studies, there is no association between COVID-19 vaccination and fertility problems in either females or males [323,324].

Thrombosis with thrombocytopenia — ChadOx1 nCoV-19/AZD1222 (AstraZeneca COVID-19 vaccine) and Ad26.COV2.S (Janssen COVID-19 vaccine, also referred to as the Johnson & Johnson vaccine) have each been associated with an extremely small risk of unusual types of thrombotic events associated with thrombocytopenia. A similar risk has not been identified with the mRNA vaccines. Many of these cases have been associated with autoantibodies directed against the platelet factor 4 (PF4) antigen, similar to those found in patients with autoimmune heparin-induced thrombocytopenia (HIT) [325-328]. Some experts refer to this syndrome as vaccine-associated immune thrombotic thrombocytopenia (VITT); others have used the term thrombosis with thrombocytopenia syndrome (TTS).

In reported cases, thrombosis often occurred at unusual sites, including the cerebral venous sinuses and mesenteric vessels, and at more than one site [329-331]. Most of the initially reported events occurred within two weeks of receipt of the initial vaccine dose and in females under 60 years of age, although subsequent cases have been reported following a longer post-vaccine interval and in males and older females. Some fatal cases have been reported.

In the United States, the risks of this syndrome following Ad26.COV2.S receipt was assessed as 3.8 cases and 0.57 deaths per million doses overall, and 9 to 10.6 cases and 1.8 to 1.93 deaths

per million doses for females 30 to 49 years old [332]. Regulatory bodies in the United States and Europe have concluded that the population and individual benefits of these vaccines (compared with no vaccination), including reductions in death and critical illness, outweigh the risk of these rare events [333-335]. Additionally, the risk of hospitalization or death associated with thrombocytopenia or thromboembolic complications associated with SARS-CoV-2 infection is higher than that associated with adenoviral vaccines [336]. Nevertheless, recipients of these vaccines should be aware of the possible association and seek immediate care for signs and symptoms suggestive of thrombocytopenia (eg, new petechiae or bruising) or thrombotic complications (including shortness of breath, chest pain, lower extremity edema, persistent severe abdominal pain, unabating severe headache, severe backache, new focal neurologic symptoms, and seizures) [335].

The incidence, risk factors, clinical features, evaluation, and management of VITT/TTS are discussed in detail elsewhere. (See "COVID-19: Vaccine-induced immune thrombotic thrombocytopenia (VITT)".)

A clear, causal relation between either of these vaccines and thromboembolic disorders overall (eg, pulmonary embolism and deep vein thrombosis) has not been identified [209,337]. For ChadOx1 nCoV-19/AZD1222, studies have reported conflicting findings regarding this risk, as discussed elsewhere. (See 'ChAdOx1 nCoV-19/AZD1222 (University of Oxford, AstraZeneca, and the Serum Institute of India)' above.)

Myocarditis — Myocarditis and pericarditis, mainly in male adolescents and young adults, have been reported more frequently than expected following receipt of the mRNA vaccines, BNT162b2 (Pfizer COVID-19 vaccine) and mRNA-1273 (Moderna COVID-19 vaccine) [338,339]. Cases were also noted in NVX-CoV2373 (Novavax COVID-19 vaccine) recipients during the phase III trials [187]. A similar pattern of cases has not been reported following receipt of Ad26.COV2.S (Janssen/Johnson & Johnson COVID-19 vaccine). Given the infrequency and the mild nature of the myocarditis and pericarditis cases, the benefits of vaccination greatly exceed the small increased risk [339]. For those who develop myocarditis or pericarditis following an mRNA vaccine or NVX-CoV2373, we suggest that any subsequent COVID-19 vaccine dose be deferred in most cases; it is reasonable for such individuals to choose to receive an additional dose (ie, the second dose of the primary series or any booster doses) once the episode has completely resolved if the risk of severe COVID-19 is high [42]. Individuals with a history of resolved myocarditis or pericarditis unrelated to COVID-19 vaccination can receive a COVID-19 vaccine.

In a review of the Vaccine Adverse Event Reporting System (VAERS), a passive surveillance system in the United States to which patients and providers can submit reports of events, among over 192 million people who had received an mRNA vaccine between December 2020

and August 2021, there were 1626 cases that met the definition of myocarditis following vaccine receipt [340]. The majority of these cases occurred after the second dose, the median age was 21 years, and 82 percent occurred in males. The estimated rate among males by age group was:

- 12 to 15 years old – 70.7 cases per million doses of BNT162b2
- 16 to 17 years old – 105.9 cases per million doses of BNT162b2
- 18 to 24 years old – 52.4 to 56.3 cases per million doses BNT162b2 and mRNA-1273, respectively

Among females of the same age groups, the estimated case rates ranged from 6.4 to 11 cases per million doses. The number of events observed exceeded the expected baseline rate among males aged 18 to 49 years and females aged 19 to 29 years.

Estimated rates of myocarditis from the Vaccine Safety Datalink (VSD), an active surveillance system in the United States, which recorded a total of 320 cases of myocarditis following 7 million vaccine doses, were somewhat higher, possibly because the system does not rely on the patients or providers to make special efforts to report cases [296]. Among males, the estimated rates of myocarditis within the week following a second vaccine dose were 150.5 cases (ages 12 to 15 years), 127.1 (ages 16 to 17 years) and 81.4 (ages 18 to 29 years) per million doses of BNT162b2 and 97.0 (ages 18 to 29 years) per million doses of mRNA-1273.

Studies from other countries have also suggested an increased rate of myocarditis following BNT162b2 vaccination compared with the expected background rate [341-344]. Observational data also suggest that the risk may be higher with mRNA-1273 than BNT162b2 [345-348].

For all age groups, the risk of myocarditis or pericarditis following mRNA vaccination is estimated in some, but not all [347], studies to be less than the risk associated with SARS-CoV-2 infection [349].

Among the cases that have been reported, most were mild [339,341,342,350]. Onset was generally within the first week after vaccine receipt. Most patients who presented for care responded well to medical treatment and had rapid symptom improvement. There have been very rare reports of fulminant myocarditis in individuals who had received an mRNA vaccine within the preceding weeks, although a causal relationship is difficult to establish [351].

The clinical presentation was illustrated in a retrospective study of 139 adolescents and young adults ≤21 years old with suspected vaccine-associated myocarditis based on elevated troponins within 30 days of vaccination without alternative diagnosis [352]. Almost all presented with chest pain, with symptom onset a median of two days after vaccine receipt. Electrocardiogram was abnormal in 70 percent (ST segment elevations or T wave

abnormalities), cardiac magnetic resonance imaging was abnormal in 77 percent (late gadolinium enhancement and myocardial edema), but systolic function on echocardiogram was normal in 80 percent. Nineteen percent were managed in the intensive care unit, although only two patients required inotropic or vasopressor support. Median hospital stay was two days, and those with decreased systolic function had normalized ejection fraction on follow-up. Ongoing monitoring is necessary to assess for long-term sequelae.

The possibility of myocarditis should be considered in adolescents and young adults who develop new chest pain, shortness of breath, or palpitations after receiving an mRNA vaccine. The possibility of other causes of myocarditis (including SARS-CoV-2 infection) should also be considered. The diagnosis and management of myocarditis are discussed in detail elsewhere. (See "Clinical manifestations and diagnosis of myocarditis in children" and "Clinical manifestations and diagnosis of myocarditis in adults" and "Treatment and prognosis of myocarditis in children" and "Treatment and prognosis of myocarditis in adults".)

Guillain-Barre syndrome — A potential association between the adenovirus vector vaccines (Ad26.COV2.S [Janssen/Johnson & Johnson COVID-19 vaccine] and ChAdOx1 nCoV-19/AZD1222 [AstraZeneca COVID-19 vaccine]) and Guillain-Barre syndrome (GBS) is being investigated, but a causal relationship has not been established. A similar signal has not been observed with the mRNA COVID-19 vaccines. The US Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC) and European regulators affirm that the benefits of these vaccines outweigh their risks [353,354]. Cases of GBS, including recurrent cases, have also been reported in the setting of SARS-CoV-2 infection [355,356], and observational data suggest the risk of GBS after infection exceeds the risk after vaccination [357]. Pending additional data, for individuals with a documented history of GBS, we suggest using COVID-19 vaccines other than adenovirus vector vaccines; if only an adenovirus vector vaccine is available, we individualize the decision to administer it based on that person's risk for severe COVID-19 and GBS history. The general approach to vaccination in individuals with a history of GBS is discussed elsewhere. (See "Guillain-Barré syndrome in adults: Treatment and prognosis", section on 'Subsequent immunizations'.)

- In the United States, as of July 24, 2021, there had been 132 preliminary reports of GBS among Ad26.COV2.S recipients after approximately 13.2 million doses [358]. The estimated rate was 9.8 cases per million doses, a rate that is approximately four times the background rate. The median age was 56 years (interquartile range 45 to 62 years), the median time to onset was 13 days following vaccination, 35 percent had a life-threatening case, and 1 patient died. In an earlier report of 100 cases, a quarter of the patients reported bilateral facial weakness [359]. Another analysis suggested an incidence of 32

cases per 100,000 person-years within the three weeks following Ad26.COV2.S receipt; the estimate for mRNA vaccines was 1.3 per 100,000 person-years [360].

- In Europe, a total of 227 cases of GBS in ChAdOx1 nCoV-19/AZD1222 recipients had been reported to regulators as of June 27, 2021, at which point approximately 51 million doses had been administered [354]. Other scattered reports have also described GBS, including variant GBS with bilateral facial weakness, following ChAdOx1 nCoV-19/AZD1222 vaccination [361,362]. However, in a cohort study including over 4 million individuals who received ChAdOx1 nCoV-19/AZD1222, the rate of GBS following the vaccine dose was not higher than the expected pre-pandemic background rate [363].

STEPS TO VACCINE AVAILABILITY AND DELIVERY

- **Establishing efficacy and licensing a vaccine** – Initial estimates of vaccine efficacy are established by phase III trials. In the United States, the minimum criteria for licensure defined by the US Food and Drug Administration (FDA) were at least 50 percent efficacy in preventing microbiologically confirmed symptomatic SARS-CoV-2 infection, with a lower bound of a 95% confidence interval of 30 percent, and at least six months of follow-up for safety assessment [364]. The World Health Organization (WHO) has proposed the same minimal efficacy targets [365].

  Once safety and efficacy meeting the criteria have been demonstrated, the FDA makes decisions on vaccine licensure, relying on guidance from the Vaccines and Related Biologic Products Advisory Committee (VRBPAC), a standing advisory group of experienced clinicians, vaccine experts, epidemiologists, and other subject matter experts. Similar approaches are taken by regulatory bodies in Canada and European countries for the licensure of their vaccines.

  In addition to the traditional process to issue a license for a vaccine, the FDA can issue an emergency use authorization (EUA), which is designed to make products available during public health emergencies [366]. For a COVID-19 vaccine to receive EUA, it must meet the prespecified efficacy criteria defined for the primary endpoint with a median of two months of follow-up for half of the trial participants [367].

- **Allocation priorities** – When vaccine supplies are limited, it is essential that vaccine deployment be equitable and efficient. Several expert organizations have released guidance documents for vaccine allocation approaches that maximize the individual and societal benefits of vaccination [368-370]. These prioritize vaccination according to risks of

acquiring infection, severe morbidity and mortality, negative societal impact (eg, if essential critical societal functions depend on an individual or groups of individuals), and transmission to others; they also emphasize equitable vaccine allocation to populations disproportionately impacted by the pandemic because of structural inequities and social determinants of health, including Black, Latin American, and Indigenous populations. The framework proposed by the WHO also takes into account global equity concerns, including assurance of vaccine access to low- and middle-income countries [370].

- **Vaccine reimbursement** – In the United States, COVID-19 vaccines will be free of charge for any individual for whom the Advisory Committee on Immunization Practices (ACIP) recommends vaccination [371]. Vaccine providers can get administration costs reimbursed by public or private insurers, or for uninsured patients, by the Health Resources and Services Administration's Provider Relief Fund [372].

POST-LICENSURE ISSUES

Combating vaccine hesitancy — Vaccine hesitancy presents a major obstacle to achieving vaccination coverage that is broad enough to result in herd immunity and slow community transmission. In general, vaccine hesitancy has become more common worldwide and was cited by the World Health Organization (WHO) as a top 10 global health threat in 2019 [373]. With COVID-19 vaccines, the accelerated nature of development and misinformation have further contributed to concerns or skepticism about safety and utility among vaccine-hesitant individuals. Efforts to optimize COVID-19 vaccine uptake should identify reasons for and characteristics associated with vaccine refusal and use that information to tailor approaches to individuals and populations.

Based on evidence from other vaccines, health care providers can improve vaccine acceptance in individual patients by making direct recommendations for vaccination, identifying concerns, educating patients on vaccine risks and benefits, and dispelling misconceptions about the disease and the vaccine. (See "Standard childhood vaccines: Parental hesitancy or refusal", section on 'Target education'.)

Communication points that may be helpful when speaking with patients who are uncertain about whether to receive a COVID-19 vaccine can be found here or on the Centers for Disease Control and Prevention (CDC) website [374,375].

Willingness to accept a COVID-19 vaccine has varied by country [376]. In the United States, rates of vaccine hesitancy have decreased over the course of the pandemic but remain substantial

[377-380].

COVID-19 vaccine hesitancy has been associated with younger age (eg, <60 years old), lower levels of education, lower household income, rural residence, and lack of health insurance [377,381-383]. In a CDC survey, the main reasons for reporting non-intent to receive vaccine were concerns about vaccine side effects and safety and lack of trust in the process [381].

Ongoing safety assessment — Adequately assessing vaccine safety is critical to the success of immunization programs. Although existing comprehensive systems to monitor vaccine safety are in place, they are being enhanced for the rollout of the COVID-19 vaccine program. It is particularly important to identify rare adverse events that are causally related to vaccine administration and assess their incidence and risk factors to inform potential vaccine contraindications.

In the United States, there are several systems in place to assess safety in the post-licensure setting; some are passive (ie, rely on others reporting the event) and others are active (ie, review databases or conduct studies to identify events) [384]. These include the Vaccine Adverse Event Reporting System (VAERS), a passive surveillance system in which providers, parents, and patients report adverse events. VAERS is intended to raise hypotheses about whether receipt of a vaccine could cause the adverse event rather than evaluate causation. The Vaccine Safety Datalink (VSD) is a collaborative project between the CDC's Immunization Safety Office and eight health care organizations to actively monitor the safety of vaccines and conduct studies about rare and serious post-vaccination adverse events. The Clinical Immunization Safety Assessment project (CISA) is a national network of vaccine safety experts from the CDC's Immunization Safety Office, seven academic medical research centers, and subject matter experts, and it provides a comprehensive vaccine safety public health service to the nation.

In addition, specific post-licensure vaccine safety systems have been implemented for the introduction of COVID-19 vaccines, similar to those established during the 2009 H1N1 influenza pandemic [385,386]. These systems will be coordinated through the CDC and will enlist multiple other health care groups to provide ongoing data on vaccine safety. These systems and information sources add an additional layer of safety monitoring [387,388].

- **V-SAFE** is a new smartphone-based health checker for people who have received a COVID-19 vaccine. The CDC will send text messages and web-based surveys to vaccine recipients through V-SAFE to check in regarding health problems following vaccination. The system will also provide telephone follow-up to anyone who reports clinically significant adverse events.

- **Enhanced reporting through National Healthcare Safety Network (NHSN) sites** – A monitoring system for health care workers and long-term care facility residents that reports to the VAERS.

- **Monitoring of larger insurer/payer databases through the US Food and Drug Administration** – A system of administrative and claims-based data for surveillance and research.

Since most vaccine-preventable diseases are transmitted person-to-person, effective vaccination not only protects the recipient but also indirectly protects others who cannot be vaccinated or do not respond adequately by preventing another source for transmission ("herd immunity") [389]. Therefore, if someone is injured by vaccine, society owes that person compensation. This is the basis for the National Vaccine Injury Compensation Program (NVICP) [390]. This program also reduces liability for the vaccine provider and the manufacturer, since it is a no-fault alternative to the traditional legal system for resolving vaccine injury claims. With COVID-19 vaccines, another compensation system called the Countermeasures Injury Compensation Program (CICP) may be used [391].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: COVID-19 – Index of guideline topics".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: COVID-19 vaccines (The Basics)" and "Patient education: COVID-19 overview (The Basics)" and "Patient education: COVID-19 and pregnancy (The Basics)" and "Patient education: COVID-19 and children (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Antigenic target** – The primary antigenic target for COVID-19 vaccines is the large surface spike protein (figure 1), which binds to the angiotensin-converting enzyme 2 (ACE2) receptor on host cells (figure 2). (See 'General principles' above.)

- **Indications** – Several vaccines using different platforms (figure 3) have high vaccine efficacy against laboratory-confirmed symptomatic COVID-19 and substantially reduce the risk of severe COVID-19 (table 2). (See 'Immunogenicity, efficacy, and safety of select vaccines' above.)

  For individuals 12 years and older, we recommend COVID-19 vaccination (**Grade 1A**). For individuals 6 months to 11 years old, we also recommend COVID-19 vaccination (**Grade 1B**). (See 'Approach to vaccination in the United States' above and 'Immunogenicity, efficacy, and safety of select vaccines' above.)

- **Selection and administration of the primary series** – In the United States, the following COVID-19 vaccines are available (table 2) (see 'Indications and vaccine selection' above and 'Dose and interval' above):

  - Two mRNA vaccines:

    - BNT162b2 (Pfizer COVID-19 vaccine): The primary series includes two intramuscular injections given at least three weeks apart for individuals aged five years or older; for children aged six months to four years old, three vaccine doses are given for the primary series. This vaccine is associated with a rare risk of myocarditis. (See 'BNT162b2 (Pfizer-BioNTech COVID-19 vaccine)' above.)

    - mRNA-1273 (Moderna COVID-19 vaccine): The primary series includes two intramuscular injections given at least one month apart for individuals six months or older. This vaccine is associated with a rare risk of myocarditis. (See 'mRNA-1273 (Moderna COVID-19 vaccine)' above.)

  For both mRNA vaccines, healthy individuals <65 years old can extend the interval between the two doses to eight weeks; this approach may be preferable for

adolescents and young adults (especially males age 12 to 39 years), as it may be associated with a lower risk of myocarditis.

- An adjuvanted recombinant protein vaccine NVX-CoV2373 (Novavax COVID-19 vaccine): The primary series includes two intramuscular injections given three to eight weeks apart for individuals aged 12 years or older. The vaccine may be associated with a rare risk of myocarditis. (See 'NVX-CoV2373 (Novavax COVID-19 vaccine)' above.)

- An adenoviral vector vaccine Ad26.COV2.S (Janssen COVID-19 vaccine, also referred to as the Johnson & Johnson vaccine): The primary series includes a single intramuscular injection for individuals 18 years or older. This vaccine is associated with a rare risk of thrombosis with thrombocytopenia and possibly Guillain-Barre syndrome. (See 'Ad26.COV2.S (Janssen/Johnson & Johnson COVID-19 vaccine)' above.)

For those eligible for all vaccines, we suggest an mRNA vaccine (BNT162b2 or mRNA-1273) or NVX-CoV2373 (**Grade 2C**). All three are highly effective; experience is greatest with the mRNA vaccines. NVX-CoV2373 may be an attractive option for individuals who prefer a more established vaccine platform. We reserve Ad26.COV2.S for those who cannot use the others, as it may be less effective against severe disease than mRNA vaccines and its associated rare adverse effects appear more severe. Nevertheless, Ad26.COV2.S is an effective and safe option for most individuals if the others are unavailable or contraindicated. (See 'Specific safety concerns' above.)

Vaccine schedules for immunocompetent (figure 4) and immunocompromised (figure 5) adults are presented in the figures.

Different vaccines are available elsewhere; a list of vaccines that have been authorized in at least one country can be found at covid19.trackvaccines.org/vaccines. Clinicians outside the United States should refer to local guidelines for vaccine recommendations in their location. (See 'Approach to vaccination in other countries' above.)

- **Adjustments for immunocompromised patients** – For individuals with certain immunocompromising conditions (table 3), we suggest administering a three-dose primary mRNA vaccine series rather than a two-dose series (figure 5) (**Grade 2C**). Similarly, we suggest an additional mRNA vaccine dose for such individuals who previously received a single Ad26.COV2.S dose (**Grade 2C**). Immunocompromised individuals are less likely to respond adequately to routine vaccination; additional doses are associated with improved vaccine effectiveness. These additional doses do not replace the booster doses. (See 'Immunocompromised individuals' above.)

- **Booster doses** – For individuals who have received a primary COVID-19 vaccine series, we recommend administration of a booster dose when eligible (**Grade 1B**). A bivalent vaccine (either Pfizer bivalent vaccine or Moderna bivalent vaccine for those ≥5 years old) is used for the booster dose, given at least two months after the primary series. The approach to booster doses for younger children depends on the primary series received. (See 'Booster dose' above.)

  For individuals ≥5 years old who have received a primary series and prior booster doses with a monovalent vaccine, we also suggest a booster dose with a bivalent mRNA vaccine (either Pfizer bivalent vaccine for those ≥5 years old or Moderna bivalent vaccine for those ≥6 years old) at least two months after the last vaccine dose (**Grade 2C**). Individuals who have immunocompromising conditions (table 3) or would otherwise be at high risk of severe disease (eg, because of multiple medical comorbidities) and who live in regions with high or increasing rates of SARS-CoV-2 transmission are likely to benefit most from a bivalent vaccine booster.

  The intended role of a bivalent booster dose is to reverse waning immunity following a prior vaccine dose and improve the breadth of protection against SARS-CoV-2 variants. In the United States, the antigenic target of the bivalent vaccines is based on the original SARS-CoV-2 strain and the BA.4/BA.5 Omicron subvariants. (See 'Bivalent mRNA vaccine booster effectiveness and immunogenicity' above.)

- **Deviations from dosing recommendations** – If the vaccine is administered in a manner different from the recommended approach, the dose or series generally does not have to be repeated. Centers for Disease Control and Prevention (CDC) recommendations on how to manage vaccination errors or deviations are presented in the table (table 4). (See 'Dose and interval' above.)

- **Expected side effects** – Vaccine recipients should be advised that side effects are common and include local and systemic reactions, including pain at the injection site, fever, fatigue, and headache. Analgesics or antipyretics (eg, nonsteroidal anti-inflammatory drugs [NSAIDs] or acetaminophen) can be taken if these reactions develop, although prophylactic use of these agents before vaccine receipt is generally discouraged because of the uncertain impact on the host immune response to vaccination. (See 'Patient counseling' above.)

- **Contraindications and precautions** – The primary contraindications to COVID-19 vaccination are severe or immediate allergic reactions to the vaccine or any of its components. All individuals should be monitored for an immediate reaction for at least 15

minutes following vaccination. Individuals without a contraindication who have a history of anaphylaxis of any kind, an immediate allergic reaction to other vaccines or injectable therapies, or a contraindication to a COVID-19 vaccine class other than the one they are receiving should be monitored for 30 minutes. (See 'Contraindications and precautions (including allergies)' above and 'Monitoring for immediate reactions to vaccine' above.)

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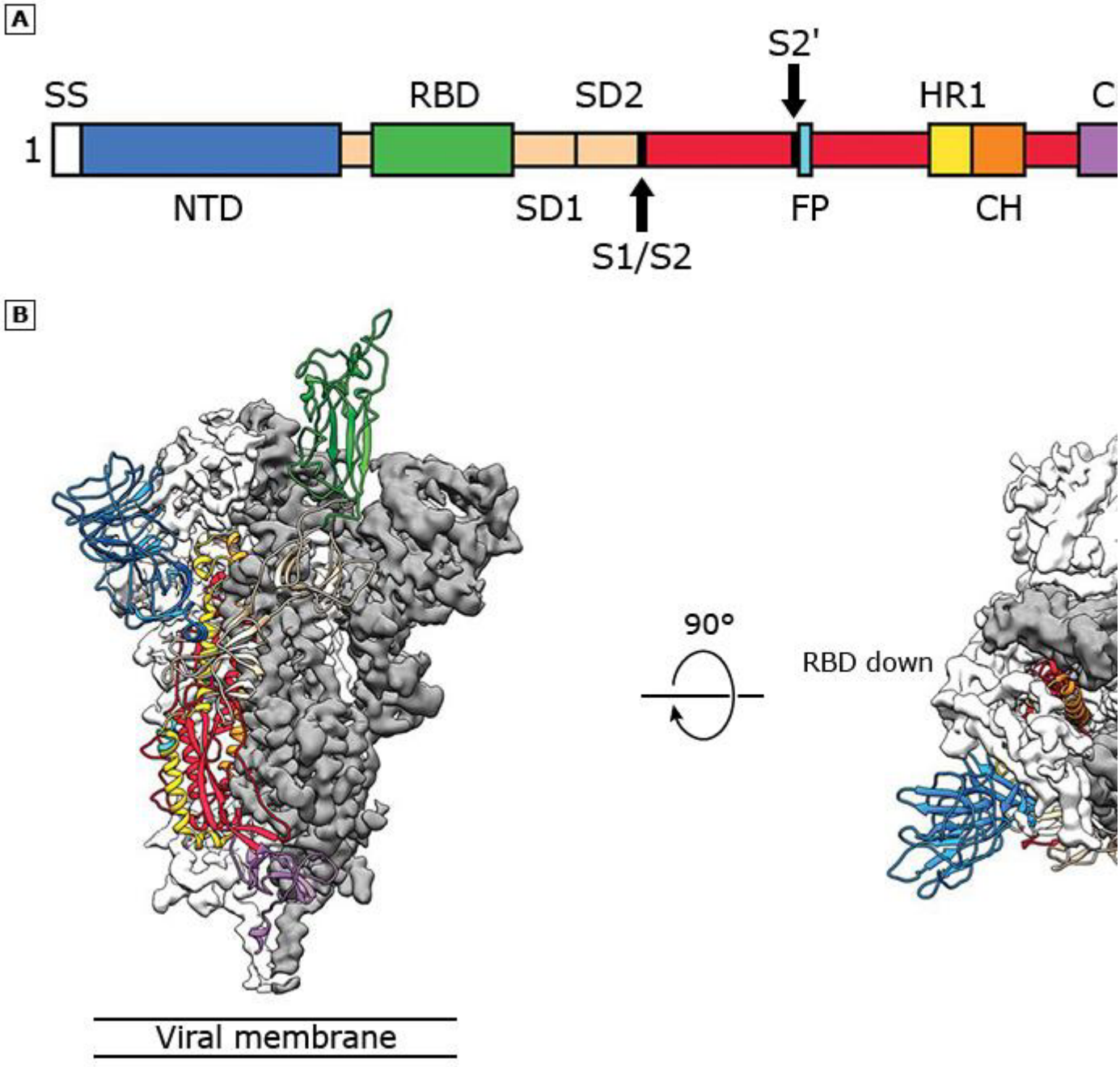
Topic 129849 Version 170.0

GRAPHICS

Structure of SARS-CoV-2 spike protein in the prefusion conformation

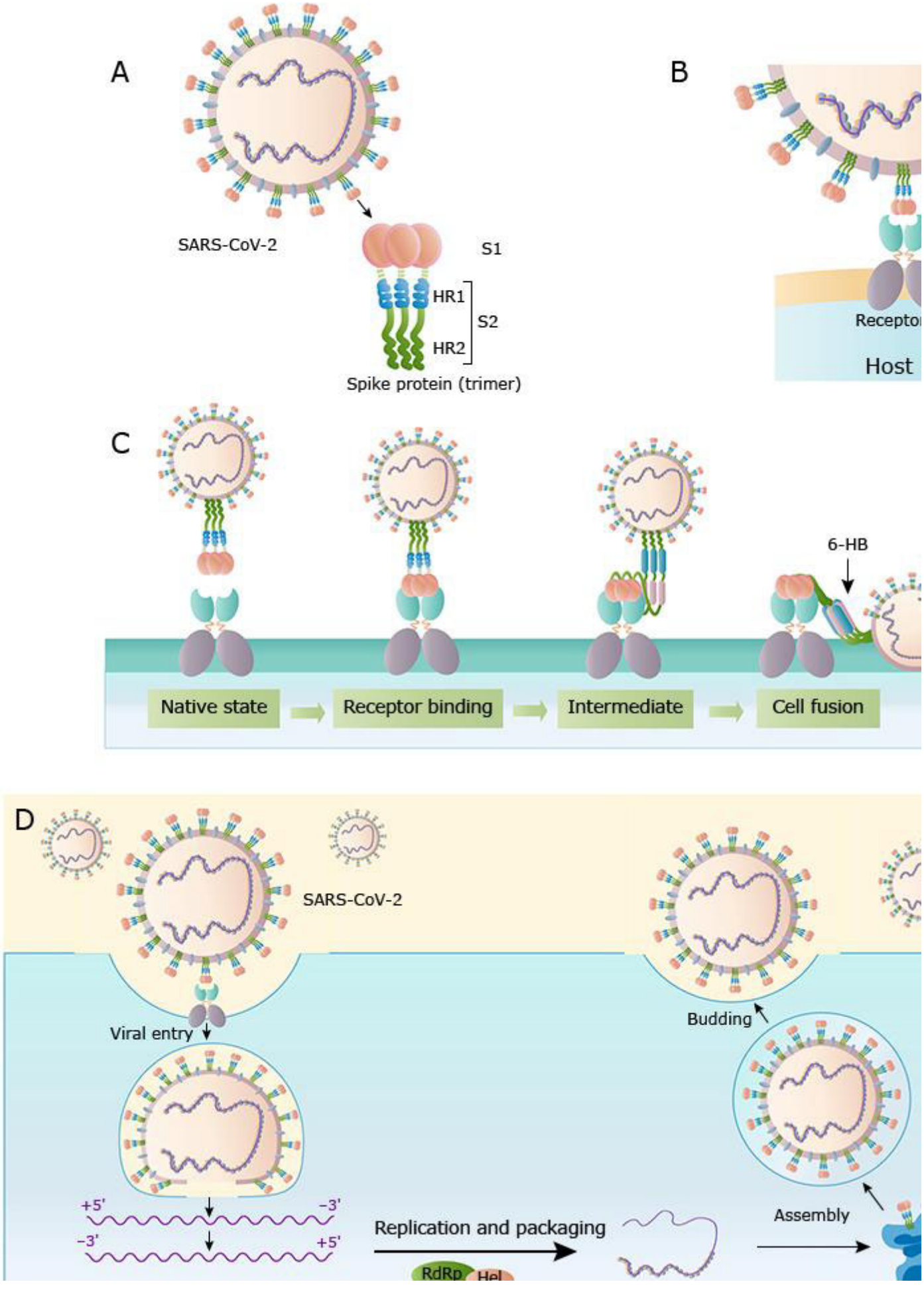


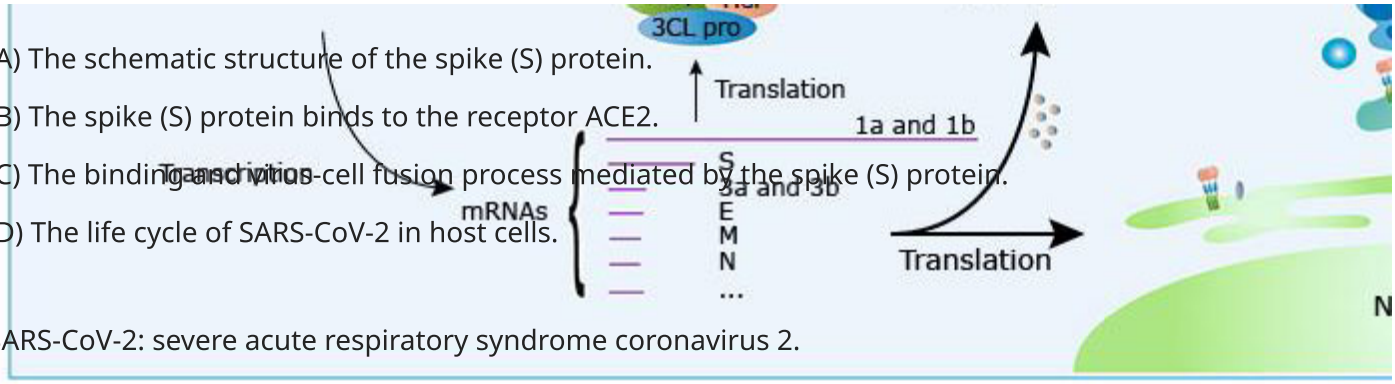
(A) Schematic of SARS-CoV-2 spike (S) protein primary structure colored by domain. Domains that were exclu
ectodomain expression construct or could not be visualized in the final map are colored white. SS: signal se
cleavage site; FP: fusion peptide; HR1: heptad repeat 1; CH: central helix; CD: connector domain; HR2: hepta
transmembrane domain; CT: cytoplasmic tail. Arrows denote protease cleavage sites.

(B) Side and top views of the prefusion structure of the SARS-CoV-2 spike (S) protein with a single receptor b the up conformation. The two RBD down protomers are shown as cryo-electron-microscopy density in eithe RBD up protomer is shown in ribbons colored corresponding to the schematic in (A).

Graphic 130132 Version 1.0

Structure and function of the SARS-CoV-2 spike protein


A
SARS-CoV-2
S1
HR1
S2
HR2
Spike protein (trimer)
B
Host
C
6-HB
Native state
Receptor binding
Intermediate
Cell fusion
D
SARS-CoV-2
Viral entry
Budding
+5'
-3'
-3'
+5'
Replication and packaging
RdRp
Assembly



(A) The schematic structure of the spike (S) protein.

(B) The spike (S) protein binds to the receptor ACE2.

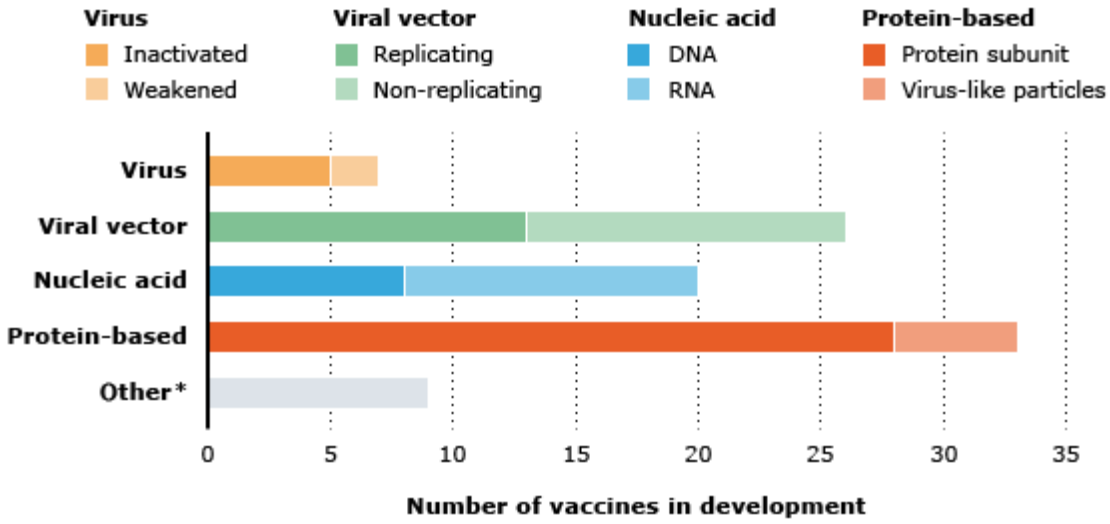
(C) The binding and virus-cell fusion process mediated by the spike (S) protein.

(D) The life cycle of SARS-CoV-2 in host cells.

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

Graphic 130134 Version 3.0

Platforms for SARS-CoV-2 vaccines in development



This reflects vaccines under development as of mid-2020. The World Health Organization maintains an updated list of COVID-19 vaccine candidates on their website.

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

* Other efforts include testing whether existing vaccines against poliovirus or tuberculosis could help to fight SARS-CoV-2 by eliciting a general immune response (rather than specific adaptive immunity) or whether certain immune cells could be genetically modified to target the virus.

Graphic 130135 Version 4.0

Vaccine platforms employed for available and candidate COVID-19 vaccines

Platform type	Description	COVID-19 vaccine examples*	Other vaccine examples	Comr
Whole virus vaccines				
Inactivated vaccines	▪ Produced by growing SARS-CoV-2 in cell culture then chemically inactivating the virus. ▪ Often combined with an adjuvant to stimulate immune response.	▪ CoronaVac (Sinovac) ▪ BBIBP-CorV/HB02 (Covilo, Sinopharm [Beijing]) ▪ Covaxin (Bharat Biotech)	▪ Hepatitis A vaccine ▪ Inactivated poliovirus vaccine	▪ Immune targets m antigens.
Live attenuated vaccines	▪ Produced by developing weakened versions of wild-type SARS-CoV-2 through genetic modification or growth in adverse conditions.	▪ COVI-VAC (Codagenix/Serum Institute of India) – in early trials	▪ Measles, mumps, rubella vaccine ▪ Varicella vaccine	▪ Immune targets m antigens. ▪ Can be ac intranasa might inc immune the site o ▪ Theoretic about rev recombir wild-type ▪ Not appr immunoc individua
Viral component vaccines				
mRNA vaccines	▪ Consist of mRNA encoding target gene.	▪ BNT162b2 (Pfizer-BioNTech vaccine) ▪ mRNA-1273 (Moderna vaccine)		▪ mRNA re cytoplasn enter nuc does not

	▪ Once administered, mRNA is translated into target protein, which elicits immune response.			or integra recipient ▪ May requ temperat
Vector virus vaccines (both replication incompetent and competent)	▪ Uses a different virus (not SARS-CoV-2) as a vector or carrier that expresses the viral protein that is the intended target.			▪ Pre-existi to the vec attenuate immunog (thus, vira that are u in humar virus vect vectors th induce se are prefe
▪ Replication-incompetent vector vaccines	▪ Viral vector has been engineered not to replicate.	▪ Ad26.COV2.S (Janssen/Johnson & Johnson) ▪ ChAdOx1 nCoV-19/AZD1222 (AstraZeneca) ▪ Gam-COVID-Vac Sputnik V (Gamaleya Institute) ▪ Ad5-nCoV (CanSino)	▪ Ad26.ZEBOV/MVA-BN-Filo (an Ebola virus vaccine)	▪ Failure of to reprod theoretic potential events th occur wit vectors. ▪ Example include a modified Ankara (M parainflu influenza adeno-as virus (AA Sendai vi
▪ Replication-competent vector vaccines	▪ Viral vector is derived from attenuated or vaccine strains of viruses.	▪ DelNS1-2019-nCoV-RBD-OPT1, an intranasal flu-based RBD vaccine (University of Hong Kong) – in trials	▪ rVSV-ZEBOV (an Ebola virus vaccine)	▪ Often res robust im response with repli incompet (stimulate immune

				▪ Can be ac intranasa might inc immune the site o ▪ Example include m vaccine s influenza vesicular virus (VS Newcastl virus (ND
Recombinant protein vaccines	▪ Composed of purified viral proteins that have been expressed in one of various systems (eg, insect and mammalian cells, yeast cells, plants).	▪ NVX-CoV2373 (Novavax)	▪ Human papillomavirus vaccines ▪ Hepatitis B vaccines	▪ Stimulate to the pu protein.
DNA vaccines	▪ Consist of plasmid DNA that contain mammalian expression promotors and the target gene, so that the target protein is expressed in the recipient.	▪ ZyCoV-D (Zydus Cadila)		▪ Are often immunog ▪ Need spe devices (e electropo

* This is not an exhaustive list of example COVID-19 vaccines and vaccine candidates for each vaccine platform. The World Health Organization maintains an updated list of vaccines in development.

COVID-19 vaccines available in the United States[1-5]

Name	Company/ developer	Platform	Indicated ages	Primary series	Booster dose*

BNT162b2	Pfizer/BioNTech	mRNA	6 months to 4 years	Three total doses[¶]: ▪ Two 3 mcg doses of monovalent vaccine 3 weeks apart ▪ One 3 mcg dose of the bivalent vaccine formulation (Pfizer-BioNTech COVID-19 vaccine, bivalent) ≥8 weeks later	Booster dose not yet authorized for individuals in this age group who have received the three-dose primary series with Pfizer-BioNTech COVID-19 vaccine
			5 to 11 years	Two 10 mcg doses 3 weeks apart[¶ Δ]	One 10 mcg dose of the bivalent vaccine formulation (Pfizer-BioNTech COVID-19 vaccine, bivalent) at least 2 months following the last vaccine dose
			12 years and older	Two 30 mcg doses 3 weeks apart[Δ]: ▪ Healthy individuals <65 years old can extend the interval to 8 weeks[◇]	One 30 mcg dose of the bivalent vaccine formulation (Pfizer-BioNTech COVID-19 vaccine, bivalent) at least 2 months following the last vaccine dose

mRNA-1273	Moderna	mRNA	6 months to 5 years	Two 25 mcg doses 4 weeks apart[Δ]	One 10 mcg dose of the bivalent vaccine formulation (Moderna COVID-19 vaccine, bivalent) at least 2 months following the last vaccine dose (for individuals who received the primary series with Moderna COVID-19 vaccine)

			6 to 11 years	Two 50 mcg doses 4 weeks apart[Δ]	One 25 mcg dose of the bivalent vaccine formulation (Moderna COVID-19 vaccine, bivalent) at least 2 months following the last vaccine dose
			12 to 17 years	Two 100 mcg doses 4 weeks apart[Δ]: ▪ Healthy individuals <65 years old can extend the interval to 8 weeks[◇]	One 25 mcg dose of the bivalent vaccine formulation (Moderna COVID-19 vaccine, bivalent) at least 2 months following the last vaccine dose
			18 years and older	Two 100 mcg doses 4 weeks apart[Δ]: ▪ Healthy individuals <65 years old can extend the interval to 8 weeks[◇]	One 50 mcg dose of the bivalent vaccine formulation (Moderna COVID-19 vaccine, bivalent) at least 2 months following the last vaccine dose
NVX-CoV2373	Novavax	Recombinant protein, adjuvanted	12 years and older	Two doses (5 mcg spike protein/50 mcg adjuvant) 3 weeks apart: ▪ Healthy individuals <65 years of age can extend the interval to 8 weeks[◇]	Use is limited to individuals 18 years and older who have not received a booster dose and are unable or unwilling to receive an mRNA vaccine[§]:

					▪ One dose (5 mcg spike protein/50 mcg adjuvant) at least 6 months after the last primary series dose
Ad26.COV2.S	Janssen/Johnson & Johnson	Replication-incompetent adenovirus 26 vector	18 years and older	One 5×10^{10} viral particles dose[Δ]	Ad26.COV2.S is not authorized as a booster dose[§]

We recommend vaccination with one of these vaccines for eligible individuals. If availability is not an issue, we suggest an mRNA vaccine (BNT162b2 or mRNA-1273) or NVX-CoV2373. Extensive data supporting the use of mRNA vaccines have accumulated since their availability. Less data on safety and efficacy of NVX-CoV2373 are available, but it is also highly effective and may be an attractive option for individuals with concerns about the novelty of the mRNA vaccine platform. We reserve Ad26.COV2.S for those who cannot use the others, as it may be less effective against severe disease than mRNA vaccines and its associated rare adverse effects appear more severe. However, if other vaccines are not available or appropriate because of contraindications, we recommend vaccination with Ad26.COV2.S rather than forgoing COVID-19 vaccination. This approach is consistent with recommendations from the United States Centers for Disease Control and Prevention.

COVID-19: coronavirus disease 2019; CDC: Centers for Disease Control and Prevention.

* The CDC recommends a booster dose with a bivalent mRNA COVID-19 vaccine for all individuals ≥5 years old who had received a primary vaccine series (including those who had also received booster doses with the monovalent vaccine); recommendations for younger children depend on the primary vaccine series received. These recommendations replaced prior recommendations regarding first and second boosters with the monovalent vaccines. Monovalent mRNA vaccines are no longer recommended for booster doses.

¶ The formulations for children are specific to the age group and are distinct from that used in older individuals.

Δ For certain immunocompromised patients, additional doses are recommended as part of the primary series. The mRNA vaccines are given as a 3-dose series rather than a 2-dose series, with the third dose given at least 4 weeks after the second; for those who received a single dose of Ad26.COV2.S, an additional dose of an mRNA vaccine is given at least 4 weeks later. These additional doses do not replace the booster dose, which is also given for those age 5 years and older.

◇ Extending the interval to 8 weeks between vaccine doses may be preferable for adolescents and young adults (especially males age 12 to 39 years) who have no major comorbidities and do not need to maximize protection within a shorter period of time; it may be associated with a lower risk of myocarditis and slightly improved effectiveness.[6]

§ Individuals who received NVX-CoV2373 or Ad26.COV2.S for the primary series should receive a bivalent mRNA vaccine booster, either the Pfizer-BioNTech COVID-19 vaccine, bivalent (if ≥5 years old) or the Moderna COVID-19 vaccine, bivalent (if ≥6 years old).

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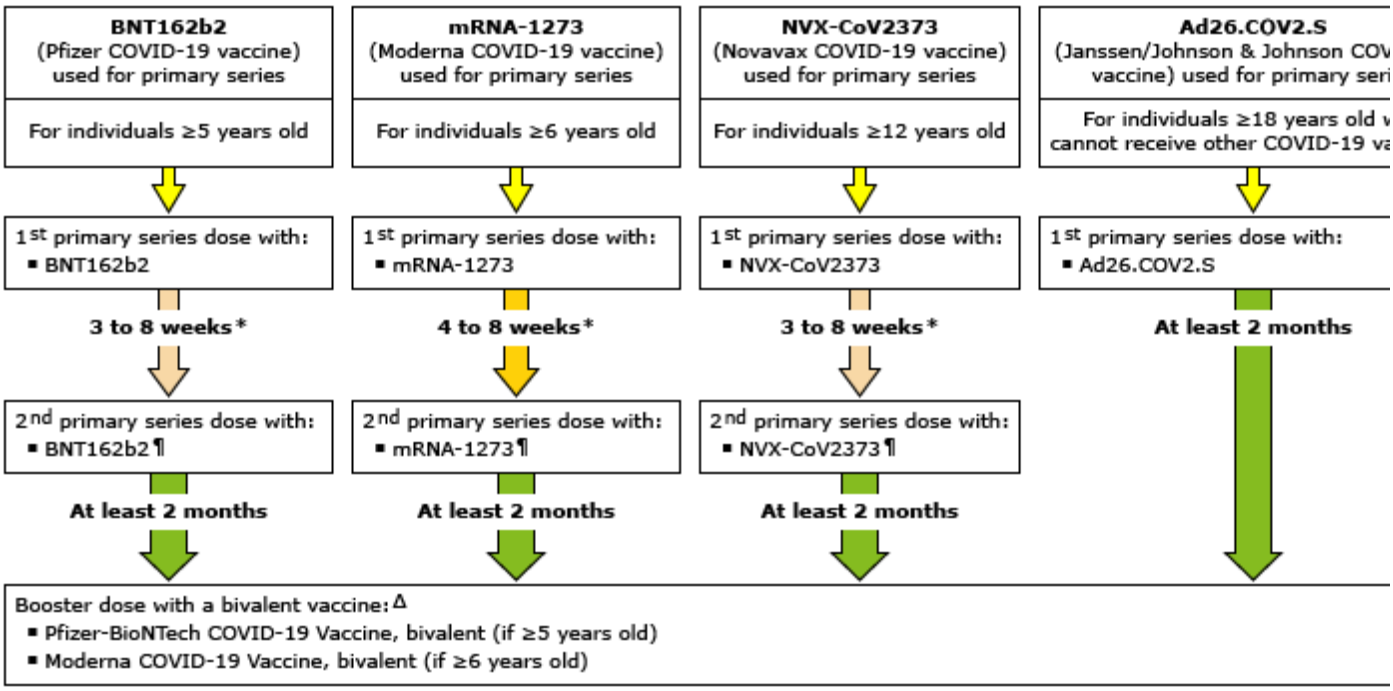
Graphic 130711 Version 41.0

COVID-19 vaccine schedule for immunocompetent adults, adolescents, and chi ≥5 years old



* A 3- to 4-week interval between primary series doses was studied in the registration trials. Healthy individ <65 years old can extend the interval to 8 weeks; this approach may be preferable for young adults (especia males 18 to 39 years old) who do not need to maximize protection within a shorter period of time.

¶ If possible, the same vaccine formulation should be used to complete the primary series. If the original va is not available or if the patient has developed a contraindication to that vaccine, a different, age-appropriat COVID-19 vaccine can be used to complete the primary series; in such cases, the second dose is given at lea weeks after the first.

Δ If the patient received monovalent booster doses in addition to the primary series, a single booster dose c bivalent vaccine is still recommended at least 2 months following the most recent monovalent vaccine dose

For individuals 18 years or older who have received a primary vaccine series but no prior booster dose and unable or unwilling to receive an mRNA vaccine, a single dose of NVX-CoV2373 can be used as a booster do least 6 months after the last primary series dose.

Graphic 138969 Version 7.0

Moderate to severe immunocompromising conditions that may result in suboptimal COVID-19 vaccine response[1,2]

Active treatment for solid tumor and hematologic malignancies
Receipt of solid-organ transplant and taking immunosuppressive therapy
Receipt of CAR-T-cell therapy or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppressive therapy)*
Moderate or severe primary immunodeficiency (eg, DiGeorge, Wiskott-Aldrich syndromes)
Advanced or untreated HIV infection (CD4 cell count <200 cells/microL, history of AIDS-defining illness without immune reconstitution, clinical manifestations of symptomatic HIV)
Active treatment with: ▪ High-dose corticosteroids (ie, ≥20 mg prednisone or equivalent per day for ≥2 weeks) ▪ Alkylating agents ▪ Antimetabolites ▪ Transplant-related immunosuppressive drugs ▪ Cancer chemotherapeutic agents classified as severely immunosuppressive ▪ TNF blockers ▪ Other biologic agents that are immunosuppressive or immunomodulatory

In the United States, the Centers for Disease Control and Prevention lists the above conditions as examples of immunocompromising conditions that warrant additional primary COVID-19 vaccine series doses (eg, a three-dose primary mRNA vaccine series rather than a two-dose primary mRNA vaccine series) and an accelerated booster dose interval. This list is not exhaustive; other immunocompromising conditions, such as impaired splenic function, may also warrant the same vaccine adjustments. Refer to other UpToDate content for specifics of vaccine doses and intervals.

People with the above conditions may also meet criteria for pre-exposure prophylaxis with specific monoclonal antibody regimens in the United States. Refer to UpToDate content on pre-exposure prophylaxis for more details.

CAR: chimeric antigen receptor; TNF: tumor necrosis factor; ACIP: Advisory Committee on Immunization Practices.

* For those who received COVID-19 vaccination prior to hematopoietic stem cell transplant or CAR-T-cell therapy, repeat vaccination with a full primary series is recommended at least 3 months after the transplant or therapy.

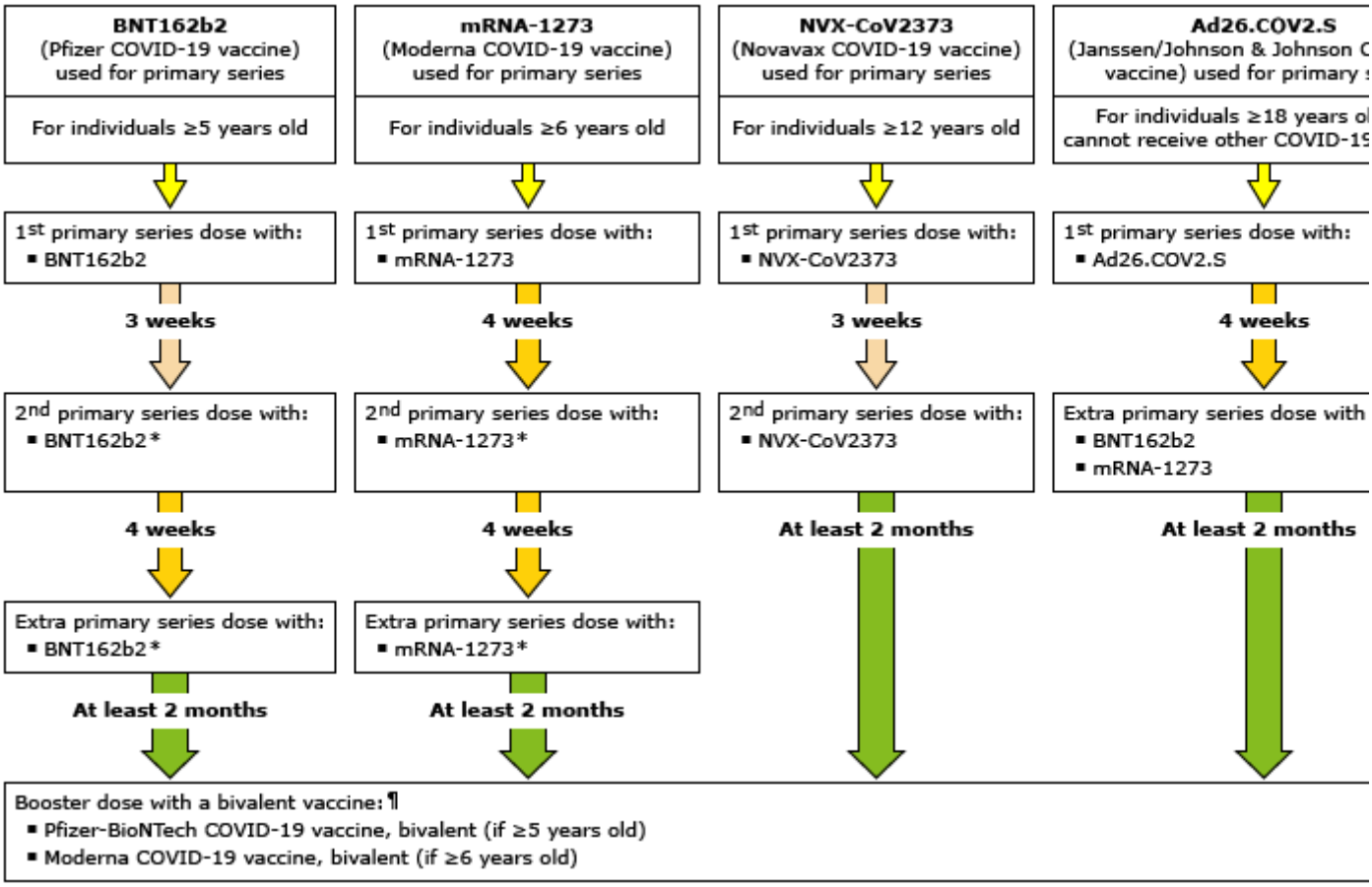
Reference:

1. *Centers for Disease Control and Prevention. Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Authorized in the United States. Available at: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html (Accessed on February 18, 2022).*
2. *US Food and Drug Administration. Fact Sheet for Healthcare Providers: Emergency Use Authorization for Evusheld (tixagevimab co-packaged with cilgavimab). Available at: https://www.fda.gov/media/154701/download (Accessed on*

December 10, 2021).

Graphic 132490 Version 7.0

COVID-19 vaccine schedule for adults, adolescents, and children ≥5 years old w moderately to severely immunocompromising conditions



Individuals with moderately to severely immunocompromising conditions have a higher risk of suboptimal response to COVID-19 vaccination. Thus, an additional primary series dose, is a strategy to improve vaccine effectiveness in this population. Such patients are also eligible for pre-exposure prophylaxis. Refer to other UpToDate content for examples of moderately to severely immunocompromising conditions that warrant th adjusted vaccination schedule.

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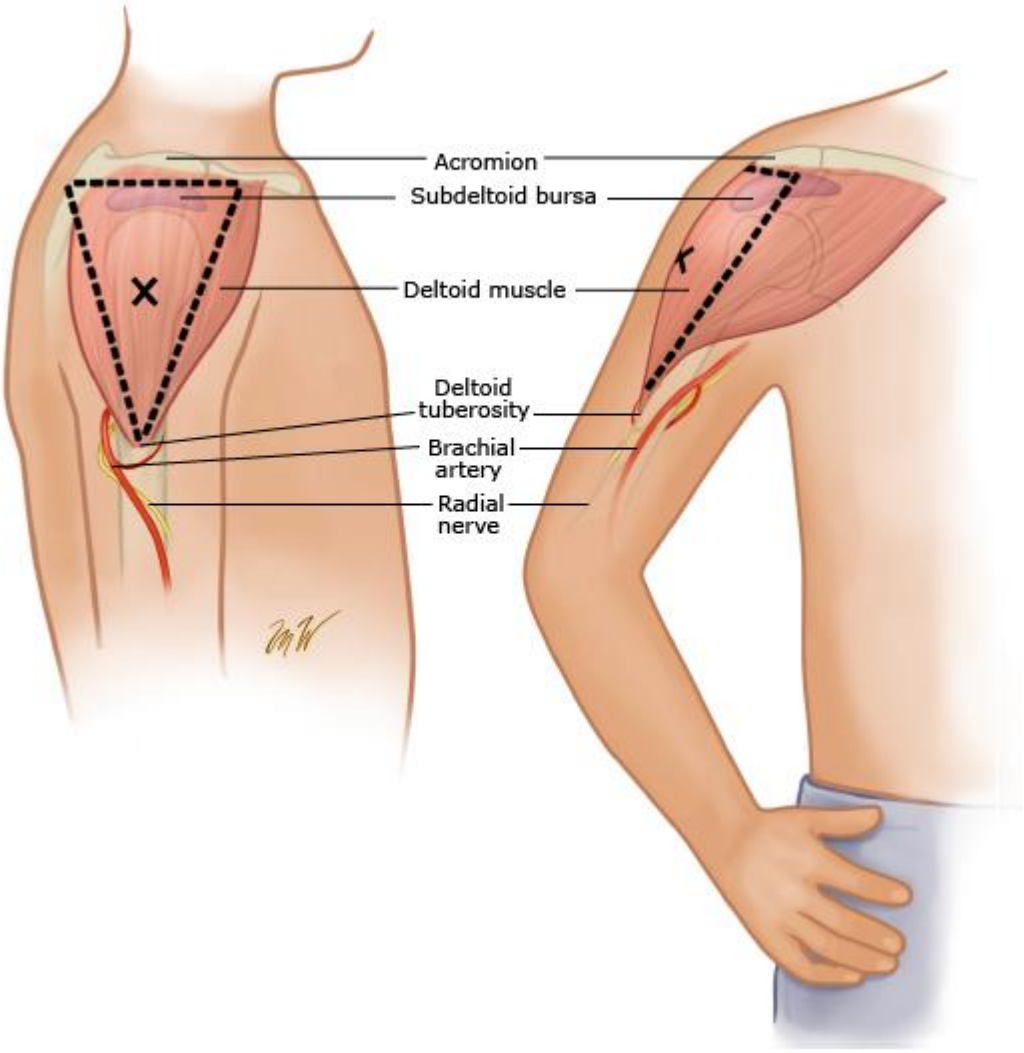
* If possible, the same vaccine formulation should used to complete the primary series. If the original vacci not available or if the patient has developed a contraindication to that vaccine, a different, age-appropriate 19 vaccine can be used to complete the primary series; in such cases, the new dose is given at least 4 weeks the last one.

¶ If the patient received monovalent booster doses in addition to the primary series, a single booster dose bivalent vaccine is still recommended, at least 2 months following the most recent monovalent vaccine dose

For individuals 18 years or older who have received a primary vaccine series but no prior booster dose and unable or unwilling to receive an mRNA vaccine, a single dose of NVX-CoV2373 can be used as a booster do least 6 months after the last primary series dose.

Graphic 138339 Version 8.0

Deltoid injection site



The arm should be completely exposed and lifted slightly out to the side (which causes the subdeltoid bursa to slide under the acromion). Identify the shoulder tip (acromion) and the deltoid tuberosity (ie, the site of insertion of the deltoid). Draw an imaginary inverted triangle between the acromion and the deltoid tuberosity. The correct injection site is in the middle one-third of this triangle (ie, in the center of the deltoid muscle, midway between the acromion and the deltoid tuberosity).

Adapted from:

1. *Administration of vaccines. In: The Australian Immunisation Handbook, 10th ed. Available at: https://immunisationhandbook.health.gov.au/vaccination-procedures/administration-of-vaccines (Accessed on September 30, 2019).*
2. *Wadman M. Vaccines on trial. Science 2017; 356:370.*

Graphic 114648 Version 4.0

Interim CDC recommendations for COVID-19 vaccine administration errors and deviations

Type	Administration error/deviation	Interim recommendation
Site/route	▪ Incorrect site (ie, site other than the deltoid muscle or vastus lateralis muscle)	▪ Do not repeat dose.
	▪ Incorrect route (eg, subcutaneous)	▪ Do not repeat dose. ▪ Inform the recipient of the potential for local and systemic adverse events.
Age	▪ Unauthorized age group (recipients younger than age 6 months)	▪ Do not give another dose at this time.*

Product and dosage	▪ Higher-than-authorized dose administered (eg, incorrect dose volume, incorrect product resulting in higher-than-authorized dose)	▪ Do not repeat dose.¶Δ
	▪ Lower-than-authorized dose administered (eg, leaked out of the syringe, equipment failure, recipient pulled away, incorrect product resulting in lower-than-authorized dose)	▪ Repeat dose immediately (no minimum interval).Δ◇ ▪ However, if a half-volume dose of vaccine is administered to a patient recommended for the full volume, another half-volume dose can be administered on the same clinic day, and the 2 doses can count as 1 full dose.
	▪ Bivalent vaccine incorrectly administered for the primary series	▪ Bivalent Pfizer-BioNTech vaccine: Do not repeat dose. ▪ Bivalent Moderna vaccine: Repeat 1 monovalent dose immediately (no minimum interval)◇ because administration of the booster dose will result in a lower-than-authorized dose.
	▪ Monovalent vaccine incorrectly administered for a booster dose (if bivalent booster indicated)	▪ In general, do not repeat dose. ▪ However, providers may administer 1 bivalent booster dose as a repeat dose based on clinical judgement and patient preference. In this case, space the repeat dose after the dose given in error by at least 2 months.

Storage and handling	▪ Dose administered after improper storage and handling (ie, temperature excursion)	▪ Contact the manufacturer for information on the stability of the vaccine.[§] If the manufacturer does not have data to support the stability of the vaccine, repeat the dose immediately (no minimum interval).[◇]
	▪ Dose administered past the expiration/beyond-use date	▪ Contact the manufacturer for information on the stability of the vaccine.[§] If the manufacturer does not have data to support the stability of the vaccine, repeat the dose immediately (no minimum interval).[◇]
Intervals	▪ Any COVID-19 dose administered prior to the minimum interval[¥]	▪ Repeat dose. Space repeat dose after the dose given in error by at least the minimum interval.[◇]
	▪ Any COVID-19 vaccine dose administered at any interval after the recommended interval	▪ Do not repeat dose. There is no maximum interval. ▪ This deviation from CDC guidance does not require VAERS reporting.
	▪ Tixagevimab/cilgavimab (Evusheld) administered less than 14 days after COVID-19 vaccination	▪ In general, do not repeat vaccine dose. However, based on clinical judgement, a repeat dose of vaccine may be administered at an interval of at least 28 days after the dose of vaccine.[◇]
Mixed primary series	▪ Incorrect COVID-19 vaccine product inadvertently administered as part of a 2- or 3-dose primary series	▪ Do not repeat dose. ▪ Any combination of Moderna, Novavax, or Pfizer-BioNTech vaccines is considered a complete primary series provided the indicated number of doses is administered. ▪ If Janssen vaccine is administered, this counts as a single-dose series and no more primary doses are indicated. ▪ Children ages 6 months to 4 years who receive different mRNA products for the first 2 doses of an mRNA COVID-19 vaccine series

		should follow a 3-dose schedule. A third dose of either mRNA vaccine should be administered 8 weeks after the second dose to complete the 3-dose primary series. ▪ Children ages 5 to 17 years who receive a mixed mRNA COVID-19 vaccine primary series can follow the Pfizer-BioNTech COVID-19 Vaccine schedule and receive a booster dose.
Diluent (Pfizer-BioNTech COVID-19 vaccine formulation only [orange cap and maroon cap])	▪ **Only** diluent administered (ie, sterile 0.9% sodium chloride)	▪ Administer the authorized dose immediately (no minimum interval).
	▪ No diluent, resulting in higher than authorized dose	▪ Do not repeat dose.[¶] Inform the recipient of the potential for local and systemic adverse events.
	▪ Incorrect diluent type (eg, sterile water, bacteriostatic 0.9% sodium chloride)	▪ Contact the manufacturer for information on the stability of the vaccine.[§] If the manufacturer does not have information to support the stability of the vaccine, repeat the dose immediately (no minimum interval).[◇]
	▪ Vaccine is mixed with too little diluent	▪ Do not repeat dose. Inform the recipient of the potential for local and systemic adverse events.[◇]
	▪ Vaccine is mixed with too much diluent	▪ Repeat dose immediately (no minimum interval).[◇]
	▪ Single-use vial of diluent is used to mix multiple vials of vaccine	▪ Do not repeat dose. Inform patient of the potential for bacterial infection.
Diluent (Pfizer-BioNTech COVID-19 formulation that should not be mixed with diluent, ie, gray cap)	▪ Vaccine is mixed with any diluent (ie, any type or volume of diluent)	▪ Contact the manufacturer for information on the stability of the vaccine.[§] If the manufacturer does not have information to support the stability of the vaccine, repeat the dose immediately (no minimum interval).[◇]

CDC: United States Centers for Disease Control and Prevention; VAERS: Vaccine Adverse Event Reporting System; FDA: US Food and Drug Administration; EUA: emergency use authorization.

* Do not administer the second dose until the person becomes eligible to receive vaccination (either by reaching the authorized age or if the authorization is extended to include additional age groups), even if this results in the second dose being administered after the recommended interval between doses. In addition to the minimum age, some experts suggest delaying the second dose for 8 weeks after the invalid dose based on the potential for increased reactogenicity and the rare risk of myocarditis and pericarditis from mRNA COVID-19 vaccine.

¶ If the administration error resulted in a higher-than-authorized vaccine dose, in general a subsequent dose may still be administered at the recommended interval. However, if local or systemic side effects following vaccination are clinically concerning (outside of the expected side effect profile), lead to serious adverse reactions, or are ongoing at the time of the subsequent dose, this dose might be delayed, but this decision should be assessed on a case-by-case basis.

Δ For FDA EUA dosing options for children who turn from age 4 years to 5 years (ie, Pfizer-BioNTech), age 5 years to 6 years (ie, Moderna), and age 11 years to 12 years (ie, Moderna and Pfizer-BioNTech) during vaccination, see Transitioning from a younger to older age group. If the dosing is in accordance with the FDA EUA, it is not considered an error and VAERS reporting is not indicated.

◇ Some experts suggest delaying the repeat dose for 8 weeks after the invalid dose based on the potential for increased reactogenicity and the rare risk of myocarditis and pericarditis from mRNA (ie, Moderna or Pfizer-BioNTech) and Novavax COVID-19 vaccines, particularly in groups at increased risk for myocarditis and pericarditis (eg, males ages 12 to 39 years). Individual risk for COVID-19 and the likelihood for an adverse event following vaccination should be taken into consideration when recommending a longer interval. It is acceptable to administer the repeat dose at an interval earlier than 8 weeks if the interval is not sooner than the minimal interval noted in this table.

§ As of the date of this update, current manufacturer contact information is:

- Pfizer: 1-877-VAX-CO19 (1-877-829-2619)
- Moderna: 1-866-MODERNA (1-866-663-3762)
- Janssen: US Toll Free: 1-800-565-4008; US Toll: 1-908-455-9922
- Novavax: 1-844-NOVAVAX (1-844-668-2829)

Please see the package inserts and EUA provider factsheets for the most up-to-date manufacturer information.

¥ Vaccine doses administered up to 4 days before the minimum interval may be counted and do not need to be repeated.

Reproduced from: Centers for Disease Control and Prevention. Interim Clinical Considerations for Use of COVID-19 Vaccines: Appendices, References, and Previous Updates. Available at: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us-appendix.html (Accessed on October 13, 2022).

Graphic 130956 Version 11.0

Anaphylaxis in adults: Rapid overview of emergency management

Diagnosis is made clinically:
The most common signs and symptoms are cutaneous (eg, sudden onset of generalized urticaria, angioedema, flushing, pruritus). However, 10 to 20% of patients have no skin findings.
Danger signs: Rapid progression of symptoms, respiratory distress (eg, stridor, wheezing, dyspnea, increased work of breathing, persistent cough, cyanosis), vomiting, abdominal pain, hypotension, dysrhythmia, chest pain, collapse.
Acute management:
The first and most important treatment in anaphylaxis is epinephrine. There are **NO absolute contraindications to epinephrine** in the setting of anaphylaxis.
Airway: Immediate intubation if evidence of impending airway obstruction from angioedema. Delay may lead to complete obstruction. Intubation can be difficult and should be performed by the most experienced clinician available. Cricothyrotomy may be necessary.
Promptly and simultaneously, give:
IM epinephrine (1 mg/mL preparation): Give epinephrine 0.3 to 0.5 mg intramuscularly, preferably in the mid-outer thigh. Can repeat every 5 to 15 minutes (or more frequently), as needed. If epinephrine is injected promptly IM, most patients respond to one, two, or at most, three doses. If symptoms are not responding to epinephrine injections, prepare IV epinephrine for infusion.
Place patient in recumbent position, if tolerated, and elevate lower extremities.
Oxygen: Give 8 to 10 L/minute via facemask or up to 100% oxygen, as needed.
Normal saline rapid bolus: Treat hypotension with rapid infusion of 1 to 2 liters IV. Repeat, as needed. Massive fluid shifts with severe loss of intravascular volume can occur.
Albuterol (salbutamol): For bronchospasm resistant to IM epinephrine, give 2.5 to 5 mg in 3 mL saline via nebulizer, or 2 to 3 puffs by metered dose inhaler. Repeat, as needed.
Adjunctive therapies:
H1 antihistamine*: Consider giving cetirizine 10 mg IV (given over 2 minutes) or diphenhydramine 25 to 50 mg IV (given over 5 minutes) – for relief of urticaria and itching only.
H2 antihistamine*: Consider giving famotidine 20 mg IV (given over 2 minutes).
Glucocorticoid*: Consider giving methylprednisolone 125 mg IV.
Monitoring: Continuous noninvasive hemodynamic monitoring and pulse oximetry monitoring should be performed. Urine output should be monitored in patients receiving IV fluid resuscitation for severe hypotension or shock.
Treatment of refractory symptoms:

Epinephrine infusion¶: For patients with inadequate response to IM epinephrine and IV saline, give epinephrine continuous infusion, beginning at **0.1 mcg/kg/minute** by infusion pump[Δ]. Titrate the dose continuously according to blood pressure, cardiac rate and function, and oxygenation.
Vasopressors¶: Some patients may require a second vasopressor (in addition to epinephrine). All vasopressors should be given by infusion pump, with the doses titrated continuously according to blood pressure and cardiac rate/function and oxygenation monitored by pulse oximetry.
Glucagon: Patients on beta-blockers may not respond to epinephrine and can be given glucagon 1 to 5 mg IV over 5 minutes, followed by infusion of 5 to 15 mcg/minute. Rapid administration of glucagon can cause vomiting.

Instructions on how to prepare and administer epinephrine for IV continuous infusions are available as separate tables in UpToDate.

IM: intramuscular; IV: intravenous.

* These medications should not be used as initial or sole treatment.

¶ All patients receiving an infusion of epinephrine and another vasopressor require continuous noninvasive monitoring of blood pressure, heart rate and function, and oxygen saturation.

Δ For example, the initial infusion rate for a 70 kg patient would be 7 mcg/minute. This is consistent with the recommended range for non-weight-based dosing for adults, which is 2 to 10 mcg/minute. Non-weight-based dosing can be used if the patient's weight is not known and cannot be estimated.

Adapted from: Simons FER. Anaphylaxis. J Allergy Clin Immunol 2010; 125:S161.

Graphic 58346 Version 33.0

SARS-CoV-2 Variants of Concern: Omicron sublineages[1-6]

Omicron sublineage (parent sublineage)	Therapeutic/prophylactic monoclonal antibodies			
	Tixagevimab-cilgavimab	**Bebtelovimab (no longer recommended)**	**Sotrovimab (no longer recommended)**	**Casirivimab-imdevimab (no longer recommended)**
BA.1	**Reduced activity**	**Active**	**Active**	Inactive
BA.2	**Active**	**Active**	Inactive	Inactive
BA.4/BA.5	**Reduced activity**	**Active**	Inactive	Inactive
BA.4.6 (BA.4)	Inactive	**Likely active**	Inactive	Inactive
BA.2.75.2 (BA.2)	Inactive*	**Likely active**	Inactive	Inactive
BQ.1/BQ.1.1 (BA.5)	Inactive	Inactive	Inactive	Inactive
XBB/XBB.1/XBB.1.5 (BA.2.10.1 and BA.2.75 recombinant)	Inactive	Inactive	Inactive	Inactive

"Variants of Concern" have evidence of an increase in transmissibility, greater risk of severe disease, a significant reduction in neutralization by antibodies generated during previous infection or vaccination, or reduced effectiveness of treatments or vaccines. Since 2022, Omicron (B.1.1.529) variants within evolving sublineages have been the predominant circulating variants globally. Prior Variants of Concern that are no longer circulating are the Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2) variants.

In the United States, the proportion of circulating variants in each state can be found on the CDC website.

Predicted activity of monoclonal antibodies against various SARS-CoV-2 variants is based on neutralizing assays that use pseudoviruses bearing the key spike protein mutations found in each variant. Neutralizing data are emerging for certain Omicron sublineages and are thus uncertain.

CDC: United States Centers for Disease Control and Prevention.

* For a related sublineage, BA.2.75, tixagevimab-cilgavimab appears to retain neutralizing activity.

References:

1. *National Institutes of Health. The COVID-19 Treatment Guidelines Panel's Statement on Omicron Subvariants and Anti-SARS-CoV-2 Monoclonal Antibodies. Available at: https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-omicron-subvariants/ (Accessed on November 9, 2022).*
2. *Cao Y, Jian F, Wang J, et al. Imprinted SARS-CoV-2 humoral immunity induces convergent Omicron RBD evolution. BioRxiv 2022.*

3. *Takashita E, Yamayoshi S, Fukushi S, et al. Efficacy of Antiviral Agents against the Omicron Subvariant BA.2.75. New Engl J Med 2022; 387:1236.*
4. *US Food and Drug Administration. Fact sheet for healthcare providers: Emergency use authorization for bebtelovimab. Available at: https://www.fda.gov/media/156152/download (Accessed on November 9, 2022).*
5. *US Food and Drug Administration. FDA Announces Bebtelovimab is Not Currently Authorized in Any US Region. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-announces-bebtelovimab-not-currently-authorized-any-us-region (Accessed December 1, 2022).*
6. *Imai M, Ito M, Kiso M, et al. Efficacy of Antiviral Agents against Omicron Subvariants BQ.1.1 and XBB. New Engl J Med 2023; 388:89.*

Graphic 131216 Version 20.0

Contributor Disclosures

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