Interim Clinical Considerations for COVID-19 Vaccines: Bivalent Boosters

COVID-19 Vaccination Guidance

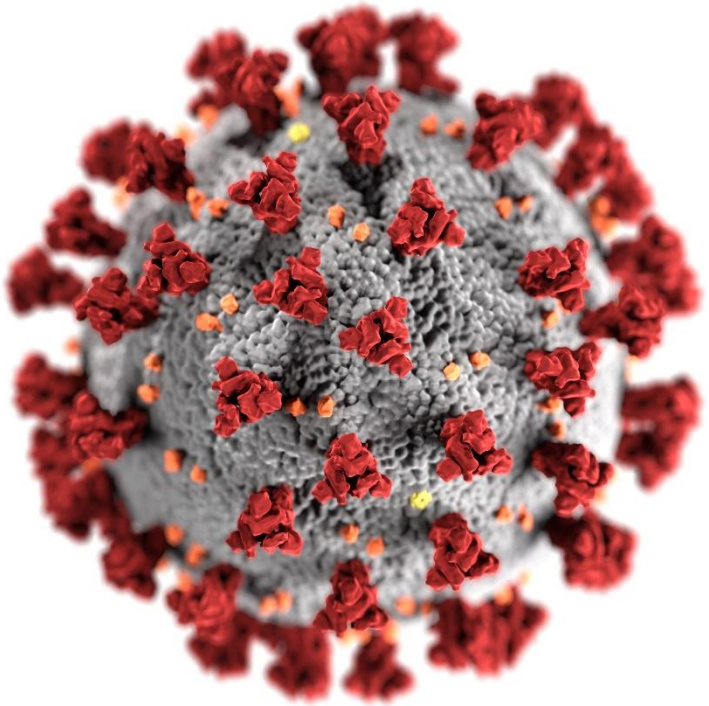
Elisha Hall, PhD

Clinical Guidelines Lead

COVID-19 Pre-exposure Prophylaxis Guidance

Evelyn Twentyman, MD, MPH

Vaccine Policy Unit Lead



ACIP Meeting
9/01/2022

cdc.gov/coronavirus

Bivalent Booster Authorized

- On August 31, 2022:
  - Moderna COVID-19 Vaccine, Bivalent authorized for use in people ages 18 years and older.
  - Pfizer-BioNTech COVID-19 Vaccine, Bivalent authorized for use in people ages 12 years and older
- Authorized as single booster dose administered at least 2 months after either:
  - Completion of primary vaccination with any authorized or approved monovalent COVID-19 vaccine, or
  - Receipt of the most recent booster dose with any authorized or approved monovalent COVID-19 vaccine

mRNA COVID-19 Vaccines No Longer Authorized as Booster Doses for People Ages 12 Years and Older

- Monovalent mRNA COVID-19 vaccines are no longer authorized as booster doses for individuals ages 12 years and older, meaning monovalent booster doses can no longer be given to people ages 12 years and older, even if the person had not previously received a monovalent booster dose.

Bivalent Booster Recommendations

- Everyone ages 12 years and older is recommended to receive 1 age-appropriate bivalent mRNA booster dose after completion of any FDA-approved or FDA-authorized monovalent primary series or last monovalent booster dose.
  - People cannot get a bivalent booster without first completing at least a primary series
  - Age-appropriate homologous and heterologous boosters allowed; there is no preference
- At this time, no changes to schedules for children ages 6 months through 11 years.

Previous Monovalent Booster Recommendations

- The bivalent booster recommendation **replaces** previous booster recommendations for people ages 12 years and older.
- This means that everyone ages 5 years and older who are eligible for a booster dose will now only be eligible for ONE booster dose.
  - People ages 5 through 11 years (who received Pfizer-BioNTech primary series): 1 monovalent booster dose
  - People ages 12 years and older: 1 bivalent booster dose

Fall Booster “Reset”

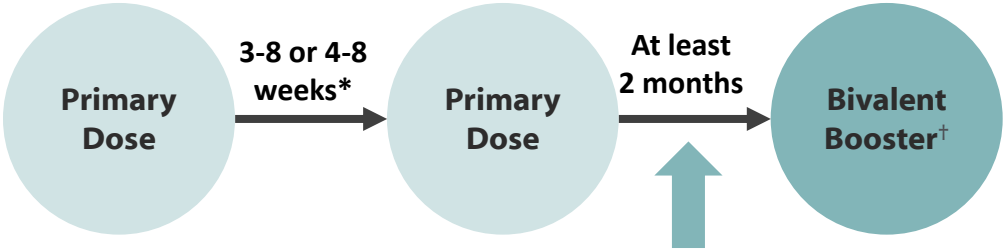
- Recommendations are simplified
- Change from dose counting to 1 bivalent booster for everyone eligible
- If eligible, a bivalent should not be denied based on total number of doses

Vaccination history	→	Next dose
Primary series	At least 2 months →	1 bivalent booster dose
Primary series + 1 booster	At least 2 months →	1 bivalent booster dose
Primary series + 2 booster	At least 2 months →	1 bivalent booster dose

COVID-19 Vaccination Schedule for People who are NOT Moderately or Severely Immunocompromised

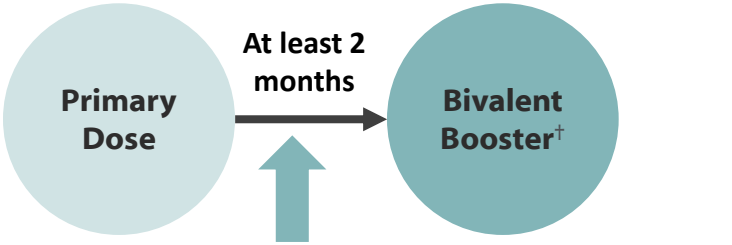
People ages 12 years and older

Moderna, Novavax, or Pfizer-BioNTech Primary Series



People ages 18 years and older

Janssen Primary Series Dose



*3-8 interval for Novavax and Pfizer-BioNTech; 4-8 interval for Moderna

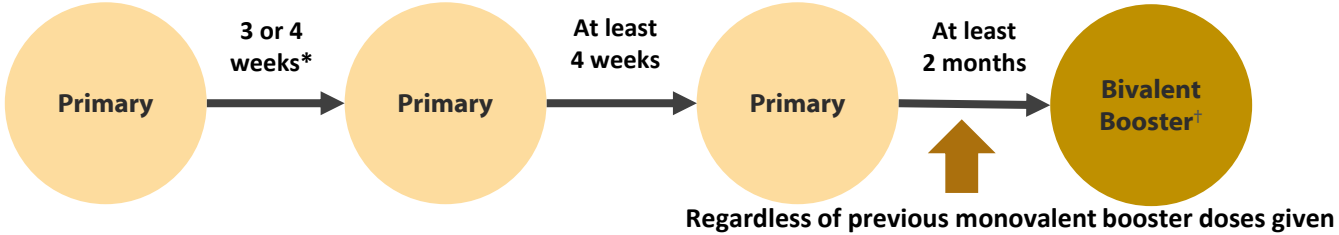
† The bivalent booster dose is administered at least 2 months after completion of the primary series.

For people who previously received a monovalent booster dose(s), the bivalent booster dose is administered at least 2 months after the last monovalent booster dose. The bivalent booster should be age appropriate; Pfizer-BioNTech is authorized for people ages 12 years and older and Moderna is authorized for people ages 18 years and older.

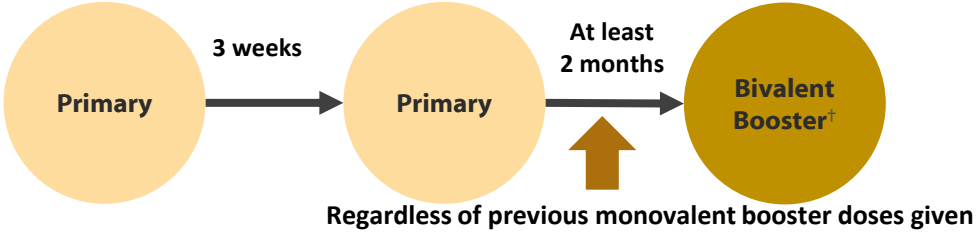
COVID-19 Vaccination Schedule for People who ARE Moderately or Severely Immunocompromised

People ages 12 years and older

Moderna or Pfizer-BioNTech Primary Series

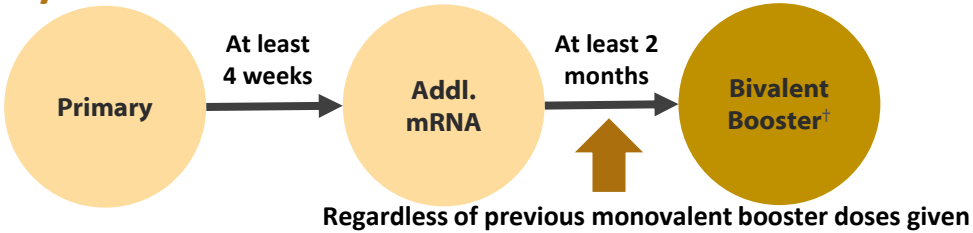


Novavax Primary Series



People ages 18 years and older who received Janssen

Janssen Primary Series Dose



*3-8 interval for Novavax and Pfizer-BioNTech; 4-8 interval for Moderna

†The bivalent booster dose is administered at least 2 months after completion of the primary series.

For people who previously received a monovalent booster dose(s), the bivalent booster dose is administered at least 2 months after the last monovalent booster dose. The bivalent booster should be age appropriate; Pfizer-BioNTech is authorized for people ages 12 years and older and Moderna is authorized for people ages 18 years and older.

Who may benefit from Evusheld?

- People ages ≥12 years:
  - With moderate to severe immune compromise
  - For whom vaccination with any available COVID-19 vaccine is not recommended due to a history of severe adverse reaction to a COVID-19 vaccine(s) and/or COVID-19 vaccine component(s)

Evusheld Healthcare Providers FS 06292022 (fda.gov)
Image: ASPR Webinar: What is Evusheld? https://aspr.hhs.gov/COVID-19/Therapeutics/Products/Evusheld/Pages/default.aspx

Tixagevimab/Cilgavimab (EVUSHELD™)

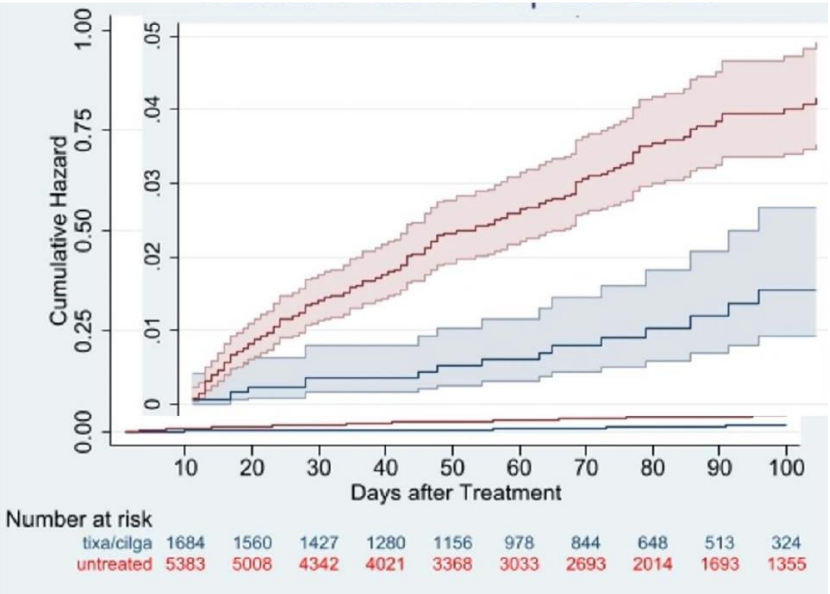
- Combination of two long-acting human monoclonal antibodies derived from B-cells donated by convalescent patients after SARS-CoV-2 infection
- **FDA's Emergency Use Authorization (EUA):**
  - Issued 12/8/21 for **pre-exposure prophylaxis** in individuals with moderate/severe immunocompromise or for whom COVID-19 vaccination is not recommended
  - Revised 2/24/22 to **increase dose to 300mg/300mg** (accounting for decreased neutralization activity against Omicron)
- Fact sheet for healthcare providers revised 6/29/22 for Evusheld to be administered **every 6 months**
- Evusheld must be prescribed by a healthcare provider
- Doses can be found through the USG therapeutic locator tool: https://covid-19-therapeutics-locator-dhhs.hub.arcgis.com/
- There are two ways for providers to order Evusheld:
  - HHS Health Partner Order Portal (HPOP), for large orders through the HPOP distribution process
  - A new direct clinical pathway established in July 2022 for Small Volume Orders of up to three doses, for providers not participating in the HPOP distribution process

Use of Evusheld is evidence-based

- A randomized clinical trial[1] and multiple retrospective and other studies[2-5] show that **Evusheld has efficacy against severe COVID-19 outcomes and provides protection against Omicron**.

- In vitro studies show that Evusheld is predicted to work against BA.4/5[6]

Figure 3. Cumulative Risk of Composite COVID-19 Outcomes for Tixagevimab-Cilgavimab Recipients Compared to Untreated Controls



1. Levin et al, Intramuscular AZD7442 (Tixagevimab-Cilgavimab) for Prevention of Covid-19, *New England Journal of Medicine*, 2022
2. Tixagevimab/Cilgavimab for Prevention of COVID-19 during the Omicron Surge: Retrospective Analysis of National VA Electronic Data | medRxiv
3. Serum neutralization of SARS-CoV-2 Omicron sublineages BA.1 and BA.2 in patients receiving monoclonal antibodies | Nature Medicine
4. Al Jurdi et al., American Journal of Transplantation;June 2022
5. Association between AZD7442 (tixagevimab-cilgavimab) administration and SARS-CoV-2 infection, hospitalization and mortality | Clinical Infectious Diseases | Oxford Academic (oup.com)
6. Takashita E, et al, Efficacy of Antibodies and Antiviral Drugs against Omicron BA.2.12.1, BA.4, and BA.5 Subvariants. N Engl J Med. 2022.

Most immunocompromised people in the US have not received Evusheld

- Number of individuals age ≥12 in the United States: **~290 million people**[2]
- Roughly **3%** of U.S. population is immunocompromised: **~8.7 million people**
- Therefore, % protected with Evusheld:

  ~5.3% of individuals who are eligible

- Supply far exceeds administration to patients: **>390,000 doses available**
- Evusheld is distributed by the US government at no cost to recipients, although there may be administration fees depending on location

Therapeutic[2]	Courses Ordered	Courses Administered
Evusheld (300 mg doses)	850,106	459,572

Data is for states, territories, and federal entities, including HRSA.

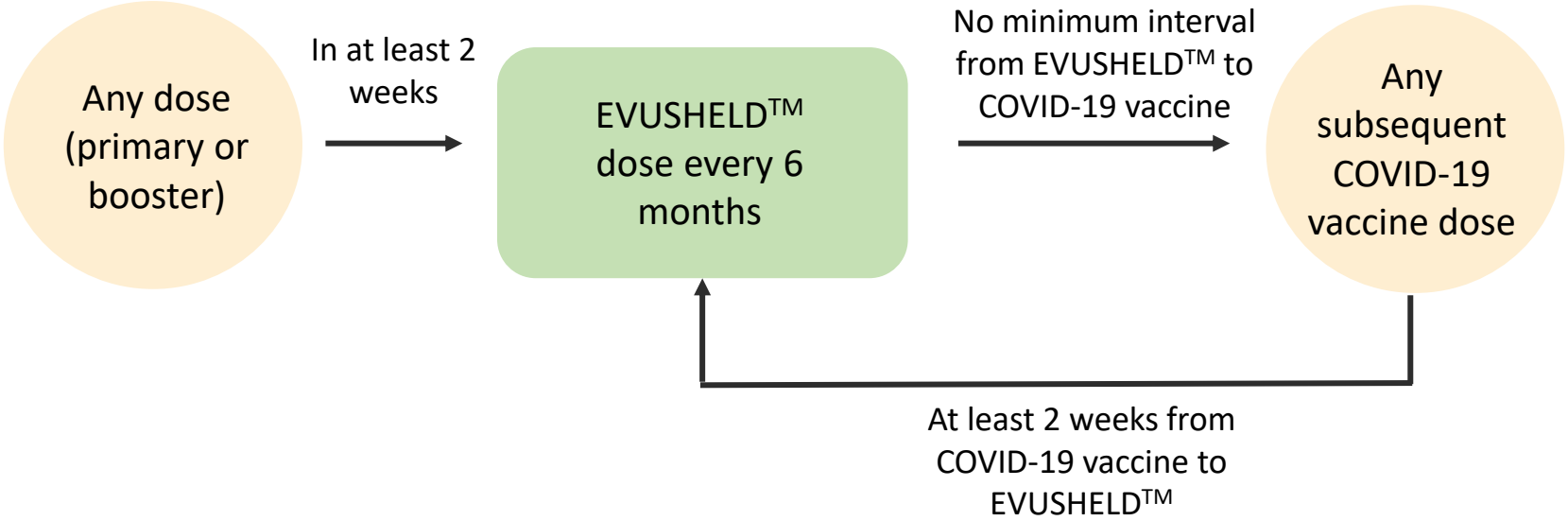
Courses administered is based on 92% of sites as of August 21, 2022

1. National population estimates: CDC wonder (wonder.cdc.gov)
2. Data source: HHS-Tiberius: https://aspr.hhs.gov/COVID-19/Therapeutics/orders/Pages/default.aspx

Supplementing COVID-19 vaccination with pre-exposure prophylaxis

Monoclonal antibodies (EVUSHELD™) for COVID-19 pre-exposure prophylaxis

People ages 12 years and older (must weigh at least 40 kg)



CDC Webpage pre-exposure prophylaxis updates for healthcare providers and the public

- Updated website content for healthcare providers:
  - Patient eligibility
  - Evusheld administration guidance
- Updated website content for the public:
  - How to know if you're eligible for Evusheld
  - How to access Evusheld
- Updated website language for Interim Clinical Considerations
  - How use of Evusheld compliments COVID-19 vaccination in people with moderate or severe immunocompromise

COVID-19 Vaccination Schedule Timing Considerations

- Timing considerations for people with current or prior SARS-CoV-2 infection
- Coadministration

Timing Considerations for People with Current or Prior SARS-CoV-2 Infection

- At a minimum, defer any COVID-19 vaccination, including bivalent booster vaccination, at least until recovery from the acute illness (if symptoms were present) and criteria to discontinue isolation have been met.
- In addition, people who recently had SARS-CoV-2 infection may consider delaying any COVID-19 vaccination, including bivalent booster vaccination, **by 3 months** from symptom onset or positive test (if infection was asymptomatic).
- Individual factors such as risk of COVID-19 severe disease, COVID-19 community level, or characteristics of the predominant SARS-CoV-2 strain should be taken into account when determining whether to delay getting a COVID-19 vaccination after infection.

Coadministration of COVID-19 Vaccines with Other Vaccines

- Routine administration of all age-appropriate doses of vaccines simultaneously is recommended as best practice for people for whom no specific contraindications exist at the time of the healthcare visit.

- Extensive experience with non-COVID 19 vaccines has demonstrated that immunogenicity and adverse event profiles are generally similar when vaccines are administered simultaneously as when they are administered alone.

- **Providers should offer all vaccines for which a person is eligible at the same visit.**

Coadministration of Influenza with COVID-19 Vaccines

- Providers should offer influenza and COVID-19 vaccines at the same visit, if eligible.
  - This includes adjuvanted or high-dose influenza vaccines; administer in separate limbs.

- With both influenza and SARS-CoV-2 circulating, getting **both vaccines** is important for prevention of severe disease, hospitalization, and death.

- Getting both vaccines at the same visit increases the chance that a person will be up to date with their vaccinations.

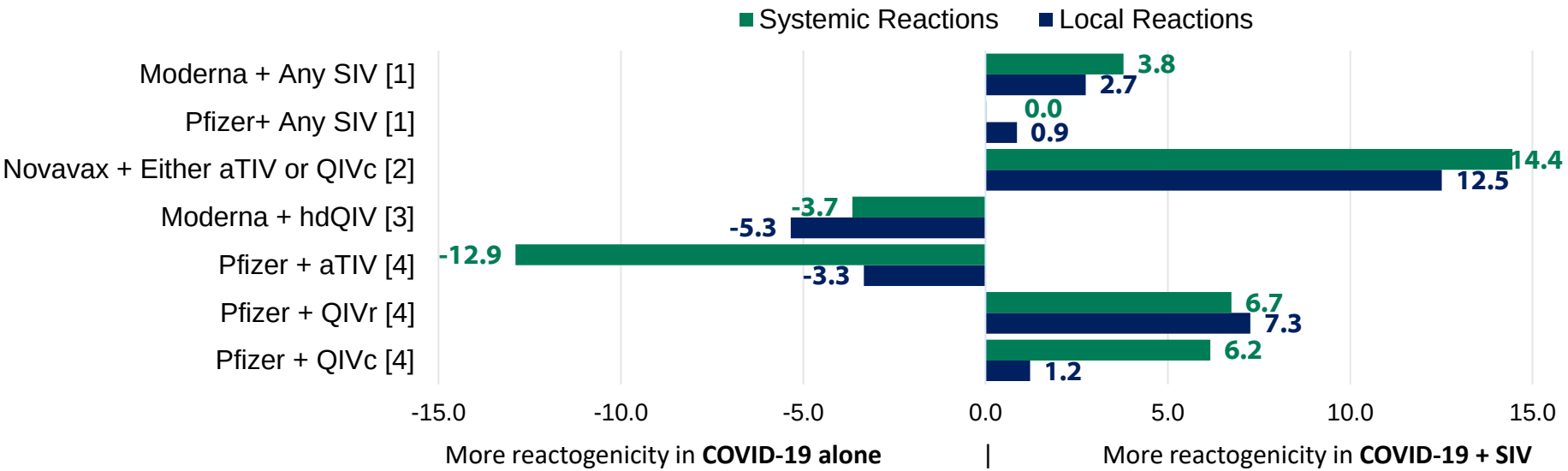
Coadministration of Influenza and COVID-19 Vaccines

- Studies looking at coadministration have shown that **immunogenicity is similar** between those who received coadministered COVID-19 vaccine and seasonal influenza vaccine (SIV) and those who received these vaccines seperately[2-4]
- 9.4% (~92,000) v-safe participants reported simultaneous vaccination with an mRNA COVID-19 vaccine and SIV[5]
- 8.7% (~454,000) of persons enrolled in the Vaccine Safety Datalink (VSD) received simultaneous vaccination with a COVID-19 booster and SIV during the 2021-2022 influenza season

1. https://www.cdc.gov/vaccines/covid-19/downloads/summary-interim-clinical-considerations.pdf
2. Lazarus R, Baos S, Cappel-Porter H, et al. Safety and immunogenicity of concomitant administration of COVID-19 vaccines (ChAdOx1 or BNT162b2) with seasonal influenza vaccines in adults in the UK (ComFluCOV): A multicentre, randomised, controlled, phase 4 trial. Lancet 2021, 398, 2277–2287.
3. Izikson R, Brune D, Bolduc JS, et al. Safety and immunogenicity of a high-dose quadrivalent influenza vaccine administered concomitantly with a third dose of the mRNA-1273 SARS-CoV-2 vaccine in adults aged ≥65 years: A phase 2, randomised, open-label study. Lancet Respir. Med. 2022.
4. Toback S, Galiza E, Cosgrove C, et al. Safety, immunogenicity, and efficacy of a COVID-19 vaccine (NVX-CoV2373) co-administered with seasonal influenza vaccines: An exploratory substudy of a randomised, observer-blinded, placebo-controlled, phase 3 trial. Lancet Respir. Med. 2021,10, 167–179.
5. Hause AM, Zhang B, Yue X, et al. Reactogenicity of Simultaneous COVID-19 mRNA Booster and Influenza Vaccination in the US. JAMA Netw Open. 2022;5(7):e2222241. Domnich A, Grassi R, Fallani E, Ciccone R, Bruzzone B, Panatto D, Ferrari A, Salvatore M, Cambiaggi M, Vasco A, Orsi A, Icardi G. Acceptance of COVID-19 and Influenza Vaccine Co-Administration: Insights from a Representative Italian Survey. Journal of Personalized Medicine. 2022; 12(2):139.

Reactogenicity of Coadministered COVID-19 Vaccine and SIV

Percent difference in participants reporting reactogenicity between COVID-19 + SIV vs COVID-19 alone



SIV: seasonal influenza vaccine; aTIV: adjuvanted trivalent influenza vaccine; QIVc: quadrivalent influenza cell-based vaccine; hdQIVc: high-dose quadrivalent influenza vaccine; QIVr recombinant quadrivalent vaccine

1. Hause AM, Zhang B, Yue X, et al. Reactogenicity of Simultaneous COVID-19 mRNA Booster and Influenza Vaccination in the US. JAMA Netw Open. 2022;5(7):e2222241.
2. Toback S, Galiza E, Cosgrove C, et al. Safety, immunogenicity, and efficacy of a COVID-19 vaccine (NVX-CoV2373) co-administered with seasonal influenza vaccines: An exploratory substudy of a randomised, observer-blinded, placebo-controlled, phase 3 trial. Lancet Respir. Med. 2021,10, 167–179.
3. Izikson R, Brune D, Bolduc JS, et al. Safety and immunogenicity of a high-dose quadrivalent influenza vaccine administered concomitantly with a third dose of the mRNA-1273 SARS-CoV-2 vaccine in adults aged ≥65 years: A phase 2, randomised, open-label study. Lancet Respir. Med. 2022.
4. Lazarus R, Baos S, Cappel-Porter H, et al. Safety and immunogenicity of concomitant administration of COVID-19 vaccines (ChAdOx1 or BNT162b2) with seasonal influenza vaccines in adults in the UK (ComFluCOV): A multicentre, randomised, controlled, phase 4 trial. Lancet 2021, 398, 2277–2287.

Reactogenicity of Coadministered COVID-19 Vaccine and SIV

- Generally, COVID-19 vaccines administered with seasonal influenza vaccine (SIV) **showed similar or slightly higher reactogenicity**, however **no specific safety concerns were identified.**

1. Hause AM, Zhang B, Yue X, et al. Reactogenicity of Simultaneous COVID-19 mRNA Booster and Influenza Vaccination in the US. JAMA Netw Open. 2022;5(7):e2222241.
2. Toback S, Galiza E, Cosgrove C, et al. Safety, immunogenicity, and efficacy of a COVID-19 vaccine (NVX-CoV2373) co-administered with seasonal influenza vaccines: An exploratory substudy of a randomised, observer-blinded, placebo-controlled, phase 3 trial. Lancet Respir. Med. 2021,10, 167–179.
3. Izikson R, Brune D, Bolduc JS, et al. Safety and immunogenicity of a high-dose quadrivalent influenza vaccine administered concomitantly with a third dose of the mRNA-1273 SARS-CoV-2 vaccine in adults aged ≥65 years: A phase 2, randomised, open-label study. Lancet Respir. Med. 2022.
4. Lazarus R, Baos S, Cappel-Porter H, et al. Safety and immunogenicity of concomitant administration of COVID-19 vaccines (ChAdOx1 or BNT162b2) with seasonal influenza vaccines in adults in the UK (ComFluCOV): A multicentre, randomised, controlled, phase 4 trial. Lancet 2021, 398, 2277–2287.

Best Practices for Multiple Injections

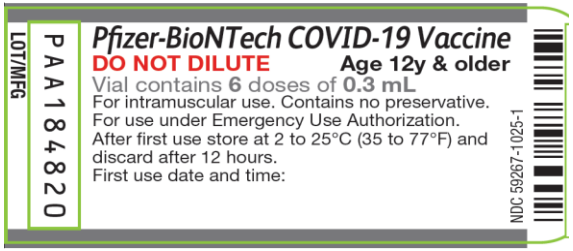
- Label each syringe with the name and the dosage (amount) of the vaccine, lot number, initials of the preparer, and exact beyond-use time, if applicable.
- Administer each vaccine in a different injection site; separate injection sites by 1 inch or more, if possible.
- Administer the COVID-19 vaccine and vaccines that may be more likely to cause a local reaction in different limbs, if possible.
  - Example: Adjuvanted or high-dose influenza vaccine and COVID-19 vaccine

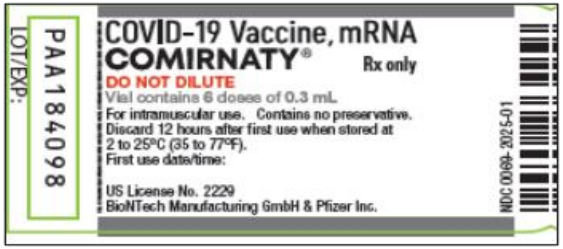
Pfizer-BioNTech COVID-19 Vaccines

	 Monovalent Product	 Bivalent Product
Authorized for ages	12 years and older	12 years and older
Authorized for doses	Primary series doses	Booster doses
Vial cap color	Gray	Gray
Dose (mRNA concentration)	30 mcg	30 mcg (15 mcg original, 15 mcg Omicron BA.4/BA.5)
Vaccine composition	Monovalent—Original	Bivalent—Original and Omicron BA.4/BA.5
Injection volume	0.3 mL	0.3 mL
Dilution required	No	No
Beyond-use date	12 hours after puncture	12 hours after puncture
Storage	Ultra-cold freezer until expiration; Refrigerator (2°C-8°C) up to 10 weeks	Ultra-cold freezer until expiration; Refrigerator (2°C-8°C) up to 10 weeks

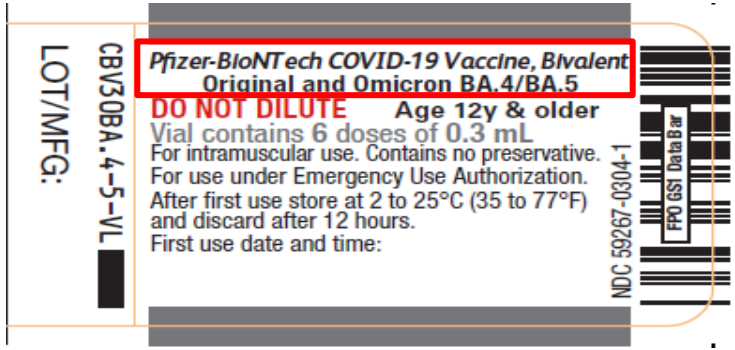
Pfizer-BioNTech Labels

Monovalent label
Primary series only
Ages 12 years and older





Bivalent label
Booster dose only
Ages 12 years and older



Moderna COVID-19 Vaccines Formulations

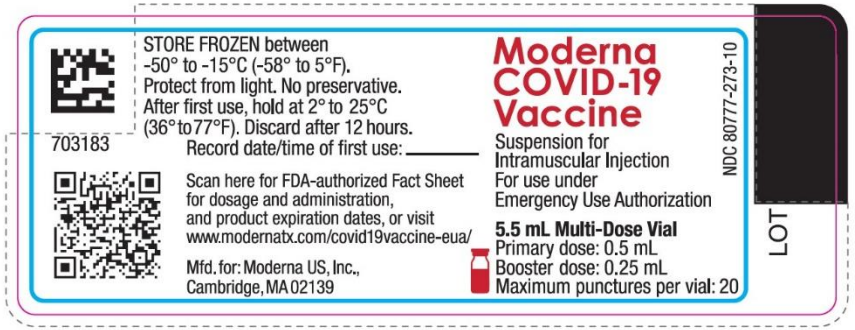
	 Monovalent Product	 Monovalent Product	 Bivalent Product
Authorized for ages	12 years and older	6–11 years	18 years and older
Vial cap color	Red	Dark blue	Dark blue
Label border color	Light blue	Purple	Gray
Dose (mRNA concentration)	100 mcg (primary dose)	50 mcg (primary dose)	50 mcg (booster dose) (25 mcg original, 25 mcg Omicron BA.4/BA.5)
Injection volume	0.5 mL	0.5 mL	0.5 mL
Dilution required	No	No	No
Beyond-use date	12 hours	12 hours	12 hours
Storage	Freezer (-15°C to -50°C) until expiration; Refrigerator (2°C to 8°C) up to 30 days	Freezer (-15°C to -50°C) until expiration; Refrigerator (2°C to 8°C) up to 30 days	Freezer (-15°C to -50°C) until expiration; Refrigerator (2°C to 8°C) up to 30 days

Moderna COVID-19 Vaccines Formulations

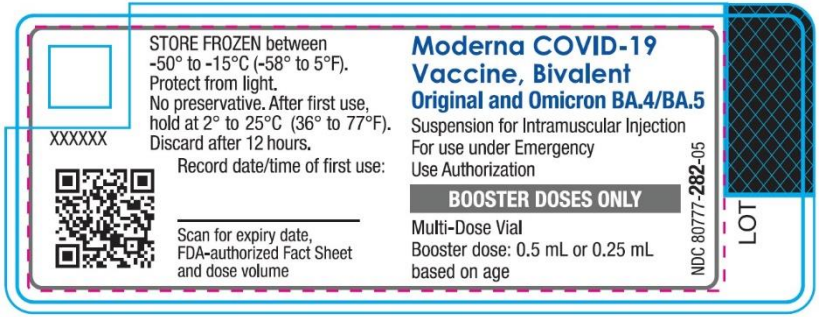
	 Monovalent Product	 Bivalent Product
Authorized for ages	12 years and older	18 years and older
Vial cap color	Red	Dark blue
Label border color	Light blue	Gray
Dose (mRNA concentration)	100 mcg (primary dose)	50 mcg (booster dose) (25 mcg original, 25 mcg Omicron BA.4/BA.5)
Injection volume	0.5 mL	0.5 mL
Dilution required	No	No
Beyond-use date	12 hours	12 hours
Storage	Freezer (-15°C to -50°C) until expiration; Refrigerator (2°C to 8°C) up to 30 days	Freezer (-15°C to -50°C) until expiration; Refrigerator (2°C to 8°C) up to 30 days

Moderna Labels

Monovalent label
Primary series only
Ages 12 years and older



Bivalent label
Booster dose only
Ages 18 years and older

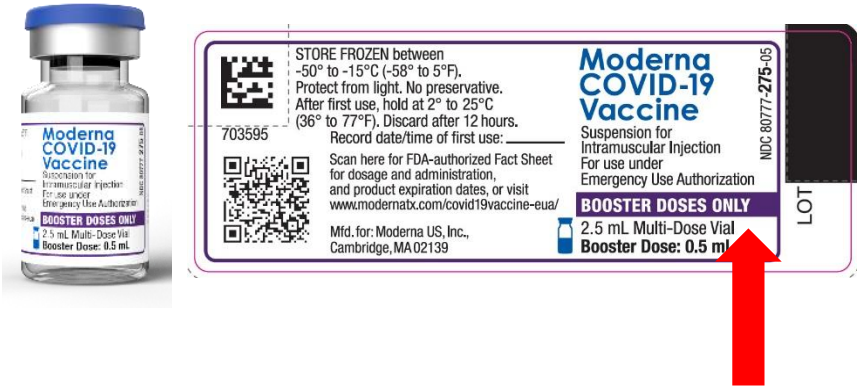


Moderna COVID-19 Vaccines Formulations

	 Monovalent Product	 Bivalent Product
Authorized for ages	6–11 years	18 years and older
Vial cap color	Dark blue	Dark blue
Label border color	Purple	Gray
Dose (mRNA concentration)	50 mcg (primary dose)	50 mcg (booster dose) (25 mcg original, 25 mcg Omicron BA.4/BA.5)
Injection volume	0.5 mL	0.5 mL
Dilution required	No	No
Beyond-use date	12 hours	12 hours
Storage	Freezer (-15°C to -50°C) until expiration; Refrigerator (2°C to 8°C) up to 30 days	Freezer (-15°C to -50°C) until expiration; Refrigerator (2°C to 8°C) up to 30 days

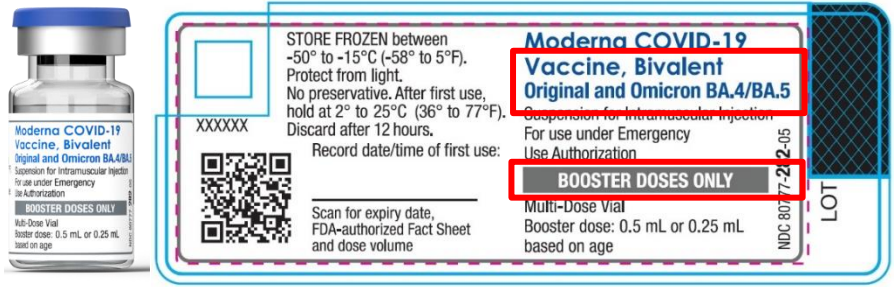
Moderna Labels

Monovalent label
Primary series only
Ages 6–11 years



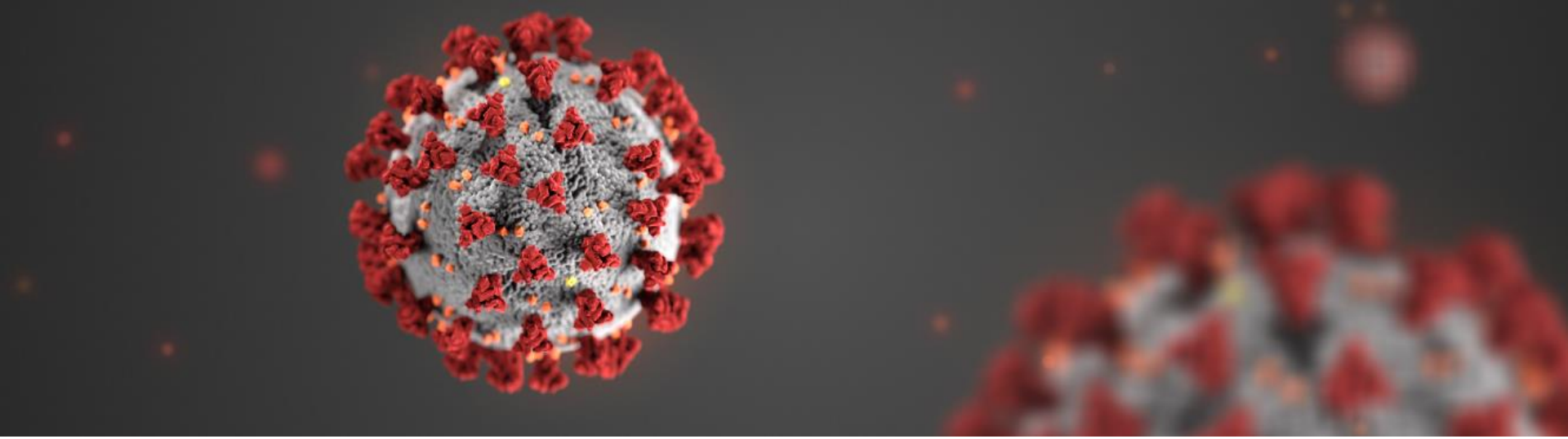
Despite label, do NOT use for booster doses

Bivalent label
Booster dose only
Ages 18 years and older



Staying Up To Date

- CDC encourages people to “Stay up to date with your COVID-19 vaccines”.
- Staying up to date keeps people current with COVID-19 vaccine recommendations.
- You are up to date if you have completed a primary series and received the most recent booster dose recommended for you by CDC.



For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.