Emergency Use Instructions for Healthcare Providers: Pfizer-BioNTech COVID-19 Vaccine for Primary, Additional, and/or Booster Doses

The Centers for Disease Control and Prevention (CDC) is issuing Emergency Use Instructions (EUI) to provide information about the use of the COVID-19 vaccine by Pfizer-BioNTech (Comirnaty), which is approved (licensed) by the Food and Drug Administration (FDA) for the prevention of COVID-19 in individuals ages 16 years and older.[1] The CDC-issued EUI provide information for the use of this vaccine that are beyond the FDA-approved labeling. The CDC-issued EUI provide information on the following uses of the COVID-19 vaccine by Pfizer-BioNTech for:

- A longer interval of 3–8 weeks between the first and second primary dose of Pfizer-BioNTech COVID-19 vaccine for persons ages 12 years and older, particularly for individuals at higher risk of mRNA COVID-19 vaccine-associated myocarditis.
- Delaying the second primary dose in persons ages 12 years and older who recently had SARS-CoV-2 infection, by 3 months from symptom onset or positive test (if infection was asymptomatic)
- Primary and/or booster dose(s), including for those with certain immunocompromising conditions or those with incomplete primary series, for persons ages 12 years and older who received primary or booster vaccination with certain non-FDA authorized or approved COVID-19 vaccines[2].
- An additional dose in persons ages 18 years and older with certain immunocompromising conditions who received primary vaccination with the Janssen COVID-19 Vaccine.
- A 3-month interval for a first booster dose after an mRNA vaccine primary series for persons ages 12 years and older who are moderately or severely immunocompromised.
- A second booster dose in persons ages 18–49 years without certain immunocompromising conditions who received both a primary dose and first booster dose with the Janssen COVID-19 Vaccine. A second booster dose in persons ages 50 years and older is authorized under EUA.
- Revaccination of moderately or severely immunocompromised persons ages 12 years and older who received certain therapies (indicated below) and received dose(s) of COVID-19 vaccine prior to or during treatment.
    - Received COVID-19 vaccine dose(s) during treatment with B-cell-depleting therapies over a limited period
    - Received COVID-19 vaccine dose(s) prior to or during treatment involving hematopoietic cell transplant (HCT) or chimeric antigen receptor (CAR)-T-cell therapy

mRNA vaccines are preferred for persons with moderate or severe immune compromise. The COVID-19 vaccine by Moderna under EUI also allow similar uses as an alternative mRNA COVID-19 vaccine to Pfizer-BioNTech, and the same or similar recommendations in the EUI also apply to the use of the COVID-19 vaccine by Moderna under EUI. See the Moderna EUI Fact Sheet for Healthcare Providers.

Refer to CDC's Interim Clinical Considerations for specific recommendations on use of the COVID-19 vaccine by Pfizer-BioNTech allowed under the EUI. Relevant information is detailed in the sections titled: "People who received COVID-19 vaccine outside the United States", "People who received COVID-19 vaccine as part of a clinical trial", and "Recommendations for COVID-19 vaccination in moderately or severely immunocompromised people." For additional information about the COVID-19 vaccine by Pfizer-BioNTech COVID-19, refer to the Comirnaty package insert or the Full Emergency Use Authorization (EUA) Prescribing Information (FDA, 2022).

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[1] Comirnaty is the proprietary name for the product licensed under the Biologics License Application (BLA). The Pfizer-BioNTech COVID-19 Vaccine has been available since December 11, 2020, pursuant to Emergency Use Authorization (EUA). The two approved formulations of Comirnaty and the two FDA-authorized formulations of Pfizer-BioNTech COVID-19 Vaccine for ≥12 years are the same formulations, and vials of the BLA-compliant vaccine may bear the name "Pfizer-BioNTech COVID-19 Vaccine." Because of these features, and because Comirnaty is commonly referred to as the "Pfizer vaccine" or the "Pfizer-BioNTech COVID-19 Vaccine," these EUI refer to this vaccine as the COVID-19 vaccine by Pfizer-BioNTech.

[2] A non-FDA authorized or approved COVID-19 vaccine that is listed for emergency use by the World Health Organization, or is included in CDC's Technical Instructions for Implementing Presidential Proclamation Advancing Safe Resumption of Global Travel During the COVID-19 Pandemic and CDC's Order, or that is a non-placebo part of a clinical trial within or outside the United States that is a WHO-EUL COVID-19 vaccine or a vaccine that is not listed for emergency use by WHO but for which a U.S. data and safety monitoring board or equivalent has independently confirmed efficacy in the United States (hereinafter "non-FDA authorized or approved COVID-19 vaccines").

What are EUI and why is CDC issuing EUI for the COVID-19 vaccine by Pfizer-BioNTech?
In 2013, the Pandemic and All-Hazards Preparedness Reauthorization Act included a new provision that allowed for the issuance of EUI to permit CDC to inform healthcare providers and recipients about certain uses of FDA-approved or cleared medical products. Specifically, EUI inform healthcare providers and recipients about such products' approved, licensed, or cleared conditions of use. The CDC Director has statutory (legal) authority to create, issue, and disseminate EUI before or during an emergency.

The COVID-19 vaccine by Pfizer-BioNTech was approved by the FDA in August 2021 as a 2-dose primary series for active immunization to prevent COVID-19 in persons ages 16 years and older. CDC is issuing these EUI to provide information about use of the COVID-19 vaccine by Pfizer-BioNTech for primary, additional, and/or booster doses that extend beyond its FDA-approved labeling as described further under "Who can receive the COVID-19 vaccine by Pfizer-BioNTech" and "What are the doses and intervals of the COVID-19 vaccine by Pfizer-BioNTech for primary, additional, and/or booster doses".

What is COVID-19?
Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the novel coronavirus, SARS-CoV-2, that emerged in late 2019. It is predominantly a respiratory illness that can affect other organs. People with SARS-CoV-2 infection have reported a wide range of symptoms, ranging from no symptoms to severe illness. Symptoms may appear 2 to 14 days after exposure to the virus. Symptoms may include fever or chills, cough, shortness of breath, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, and diarrhea.

Who can receive the COVID-19 vaccine by Pfizer-BioNTech?
The below describes who can receive the COVID-19 vaccine by Pfizer-BioNTech under EUI. The COVID-19 vaccine by Moderna can also be used under EUI for similar uses as an alternative mRNA COVID-19 vaccine (see the Moderna EUI Fact Sheet for Healthcare Providers).

- Persons ages 12 years and older, particularly those at higher risk of mRNA COVID-19 vaccine-associated myocarditis, may receive a second primary dose of the COVID-19 vaccine by Pfizer-BioNTech after a longer interval of 3–8 weeks following the first primary dose.
- Persons ages 12 years and older who recently had SARS-CoV-2 infection may receive the second primary dose after a deferral period of 3 months from symptom onset or positive test (if infection was asymptomatic)
- Persons ages 12 years and older who received an incomplete primary series (e.g., only the first dose of 2-dose primary series) with certain non-FDA authorized or approved COVID-19 vaccines should receive a primary dose of the COVID-19 vaccine by Pfizer-BioNTech.
- Persons ages 12 years and older who have received primary vaccination with certain non-FDA authorized or approved COVID-19 vaccines should receive a booster dose of the COVID-19 vaccine by Pfizer-BioNTech.
- Persons ages 18–49 years without certain immunocompromising conditions who received both a primary dose and a first booster dose of the Janssen COVID-19 Vaccine may receive a second booster dose of the COVID-19 vaccine by Pfizer-BioNTech. A second booster dose in persons ages 50 years and older is authorized under EUA.
- For certain moderately or severely immunocompromised persons:
    - Ages 12 years and older who received primary vaccination with certain non-FDA authorized or approved COVID-19 vaccines should receive an additional primary dose of the COVID-19 vaccine by Pfizer-BioNTech.
    - Ages 18 years and older who received primary vaccination with the Janssen COVID-19 Vaccine should receive an additional dose with the COVID-19 vaccine by Pfizer-BioNTech.
    - Ages 12 years and older who received certain therapies (indicated below) and received dose(s) of COVID-19 vaccine prior to or during treatment should be revaccinated with the COVID-19 vaccine by Pfizer-BioNTech for any doses received before or during treatment.

- Received COVID-19 vaccine dose(s) during treatment with B-cell-depleting therapies over a limited period
- Received COVID-19 vaccine dose(s) prior to or during treatment involving HCT or CAR-T-cell therapy

What are the doses and intervals of the COVID-19 vaccine by Pfizer-BioNTech for primary, additional, and/or booster doses?

- A second primary dose of the COVID-19 vaccine by Pfizer-BioNTech (30 µg in 0.3 mL) should be administered intramuscularly to persons ages 12 years and older; this may be 3–8 weeks after the first primary dose. The approved interval is 3 weeks after the first dose, but an 8-week interval may be optimal for some people.
- A second primary dose of the COVID-19 vaccine by Pfizer-BioNTech (30 µg in 0.3 mL) may be delayed by 3 months from symptom onset or positive test (if infection was asymptomatic) in persons ages 12 years and older who recently had SARS-CoV-2 infection
- A primary dose, including as an additional primary dose for those with certain immunocompromising conditions, of the Pfizer-BioNTech vaccine (30 µg in 0.3 mL) should be administered intramuscularly to persons ages 12 years and older at least 28 days after primary vaccination with certain non-FDA authorized or approved COVID-19 vaccines.
- A first booster dose of the COVID-19 vaccine by Pfizer-BioNTech (30 µg in 0.3 mL) should be administered intramuscularly for persons ages 12 years and older who completed an mRNA COVID-19 vaccine primary series or primary vaccination with a series that included certain non-FDA authorized or approved COVID-19 vaccines: at least 3 months after completion of primary vaccination for persons with certain immunocompromising conditions or at least 5 months after completion of primary vaccination for persons without certain immunocompromising conditions.
- A second booster dose with the COVID-19 vaccine by Pfizer-BioNTech (30 µg in 0.3 mL) may be administered intramuscularly at least 4 months after the first booster dose to persons 18–49 years of age without certain immunocompromising conditions who received both a primary dose and first booster dose with the Janssen COVID-19 Vaccine.
- An additional dose with the COVID-19 vaccine by Pfizer-BioNTech (30 µg in 0.3 mL) should be administered intramuscularly for persons ages 12 years and older with certain immunocompromising conditions at least 28 days after a primary dose with the Janssen COVID-19 Vaccine (e.g., 1 primary dose of the Janssen COVID-19 Vaccine followed by an additional dose with an mRNA COVID-19 vaccine at least 28 days after the primary dose). People who received both 1 primary dose and 1 booster dose of the Janssen COVID-19 Vaccine or 1 primary dose of the Janssen COVID-19 Vaccine followed by 1 booster dose of an mRNA COVID-19 vaccine should receive an additional dose with the COVID-19 vaccine by Pfizer-BioNTech (30 µg in 0.3 mL) at least 2 months after the booster dose.
- Revaccination with the COVID-19 vaccine by Pfizer-BioNTech for any doses received before or during treatment with certain therapies (indicated below).
    - Received COVID-19 vaccine dose(s) during treatment with B-cell-depleting therapies over a limited period: the suggested interval to start revaccination is about 6 months after completion of the B-cell-depleting therapy
    - Received COVID-19 vaccine dose(s) prior to or during treatment with HCT or CAR-T-cell therapy: revaccination at least 3 months after treatment

Refer to CDC's Interim Clinical Considerations for specific and the latest dosing recommendations (e.g., number of doses, dosing intervals, revaccination) that may vary for individuals with certain medical conditions and/or in certain circumstances, which differ from or extend beyond the FDA-authorized and/or FDA-approved labeling.

See Table 3 COVID-19 vaccination schedule for moderately or severely immunocompromised people in CDC's Interim Clinical Considerations for the latest dosing recommendations. On a case-by-case basis, providers of moderately or severely immunocompromised patients who are ages 12 years and older may administer the COVID-19 vaccine by Pfizer-BioNTech outside of the FDA-authorized or FDA-approved labeling and CDC

recommended dosing intervals based on clinical judgment when the benefits of vaccination are deemed to outweigh the potential and unknown risks for the recipient.

What are the formulations of the COVID-19 vaccine by Pfizer-BioNTech that these EUI apply to?
The EUI apply to the FDA-approved formulations of the COVID-19 vaccine by Pfizer-BioNTech. As of December 16, 2021, there are two FDA-approved formulations of this vaccine that are distinguished by purple and gray caps. They are also FDA-authorized under EUA. The multiple dose vials with purple caps contain phosphate buffered saline that must be diluted with normal saline prior to administration. The multidose vials with gray caps contain tromethamine (Tris) buffer and do not require dilution for administration. Each formulation, when prepared according to its respective formulation-specific instructions for administration, provide 0.3 mL doses (each containing 30 µg mRNA). FDA has explained that these formulations of the vaccine can be used interchangeably without presenting any safety or effectiveness concerns, when prepared according to their respective formulation-specific instructions for use.

What are the common side effects with the COVID-19 vaccine by Pfizer-BioNTech?
Adverse reactions following administration of the vaccine that have been reported in clinical trials and/or post authorization include injection site pain, fatigue, headache, muscle pain, chills, joint pain, fever, injection site swelling, injection site redness, nausea, malaise, lymphadenopathy, decreased appetite, rash, pain in extremity, diarrhea, and vomiting.

What are possible serious side effects with the COVID-19 vaccine by Pfizer-BioNTech?
Severe allergic reactions, including anaphylaxis, and other hypersensitivity reactions (e.g., rash, pruritus, urticaria, angioedema), syncope, myocarditis and pericarditis have been reported following administration of the vaccine outside of clinical trials. Myocarditis and/or pericarditis are rare, serious adverse events that have been reported after receipt of mRNA COVID-19 vaccines, with the highest risk currently observed in males ages 12–29 years.

Who should not receive the COVID-19 vaccine by Pfizer-BioNTech?
Do not administer the COVID-19 vaccine by Pfizer-BioNTech to persons with known history of a severe allergic reaction (e.g., anaphylaxis) to a previous dose or any component of the vaccine (see *Contraindications, and Warnings and Precautions* sections in the Comirnaty package insert or Full EUA Prescribing Information as well as CDC's Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Approved or Authorized in the United States for additional considerations).

What information should be provided to persons receiving a primary, additional, and/or booster dose of the COVID-19 vaccine by Pfizer-BioNTech as described in the EUI?

- Provide the EUI Fact Sheet for Recipients and Caregivers.
- Provide a CDC COVID-19 Vaccination Record Card to the recipient or their caregiver with the lot number and date of administration recorded for the primary, additional, or booster dose of the COVID-19 vaccine by Pfizer-BioNTech.
- Provide the v-safe information sheet to vaccine recipients/caregivers and encourage vaccine recipients to participate in v-safe. V-safe is a voluntary smartphone-based tool that uses text messaging and web surveys to check in with people who have been vaccinated to identify potential side effects after COVID-19 vaccination. V-safe asks questions that help CDC monitor the safety of COVID-19 vaccines. For more information, visit: www.cdc.gov/vsafe.

What is the available supporting evidence for use of the COVID-19 vaccine by Pfizer-BioNTech for additional primary or booster doses in people who received a primary vaccination with non-FDA authorized or approved COVID-19 vaccines?
CDC has not systematically evaluated the safety, immunogenicity, and efficacy of an additional dose of the COVID-19 vaccine by Pfizer-BioNTech (as either an additional primary dose for certain immunocompromised

persons or as a booster dose) following receipt of primary vaccination with a non-FDA authorized or approved COVID-19 vaccine. However, studies of COVID-19 vaccine boosting in the United Kingdom have shown that a third dose of AstraZeneca, Moderna, or Pfizer-BioNTech COVID-19 vaccines successfully boosted immune responses in people who had been primed with two doses of Pfizer-BioNTech or AstraZeneca COVID-19 vaccines approximately 3 months earlier. Levels of binding (IgG) and neutralizing antibodies, including against Delta variant, were generally higher when an mRNA vaccine was used as either a heterologous or homologous boost, or where the AstraZeneca COVID-19 vaccine was used as a heterologous boost after primary vaccination with the Pfizer-BioNTech COVID-19 vaccine (Munro et al., 2021). Frequencies of local and systemic adverse reactions in the 7 days post booster vaccination were higher with heterologous than homologous boosters and in those aged under 70 years when compared to older recipients. Frequencies of local and systemic adverse reactions were higher when the AstraZeneca COVID-19 vaccine was used to boost those who received primary vaccination with the Pfizer-BioNTech COVID-19 vaccine, when compared with the Pfizer-BioNTech COVID-19 vaccine after either primary vaccination (Munro et al., 2021).

Additional supporting evidence for use of the COVID-19 vaccine by Pfizer-BioNTech for additional primary or booster doses in people who received a non-FDA authorized or approved COVID-19 primary vaccination series are as follows. An unpublished small, randomized trial in Bahrain found that a third dose of Pfizer-BioNTech COVID-19 vaccine after a 2-dose Sinopharm BIBP COVID-19 vaccine primary series resulted in higher levels of IgG antibodies against the spike-antigen of SARS-CoV-2 (anti-S-IgG) compared to a 3-dose series of Sinopharm BIBP COVID-19 vaccine (SAGE, 2021). In a pilot prospective cohort study of healthcare workers (HCWs) from Lebanon, 50 HCWs who received a 2-dose primary series of Sinopharm BIBP COVID-19 vaccine and a single booster dose of Pfizer-BioNTech COVID-19 vaccine had significantly higher anti-S-IgG titers compared to 50 homologous vaccinees (2 primary series doses and 1 booster dose of Pfizer-BioNTech COVID-19 vaccine) (Moghnieh, 2021). A longitudinal study of 41 Thai HCWs who received a 2-dose primary series of Sinovac (CoronaVac) COVID-19 vaccine demonstrated booster antibody responses following either AstraZeneca or Pfizer-BioNTech COVID-19 vaccines, including against the Delta variant (Patamatamkul, 2021). Local and systemic reactogenicity was reported to be mild to moderate across studies. Finally, a study from Chile examining heterologous boosting with AztraZeneca or Pfizer-BioNTech among Sinovac-CoronaVac primed individuals demonstrated higher vaccine effectiveness (VE) against infection, symptomatic disease, and intensive care unit admission compared with homologous boosting (Araos, 2021).

WHO's Strategic Advisory Group of Experts (SAGE) on Immunization has noted that although data are currently limited on the safety, immunogenicity, and effectiveness of heterologous versus homologous additional doses, evolving evidence suggests that use of a heterologous vaccine for an additional dose may be more immunogenic than a homologous series. In its recommendations for an additional dose in certain immunocompromised people and in people aged 60 years and over who received Sinopharm BIBP or Sinovac-CoronaVac COVID-19 vaccines as a 2-dose primary series, WHO has advised that countries can consider heterologous additional doses based on supply availability (WHO SAGE 2021a-c).

More than 80 countries are using boosters after non-FDA authorized or approved COVID-19 vaccines. Countries such as the United Kingdom (JCVI, 2021a-b), Canada (National Advisory Committee on Vaccination, 2021), Germany, and France have recommended heterologous dosing, including with use of Pfizer-BioNTech COVID-19 vaccine, for an additional primary series and/or booster dose based on their reviews of available immunological and safety data, as well as the epidemiology of COVID-19 and other contextual factors.

The heterologous booster dose of Pfizer-BioNTech COVID-19 vaccine in individuals who completed primary vaccination with Janssen COVID-19 Vaccine is supported by the immunogenicity data from a Phase 1/2 open-label clinical study (NCT04889209) by the National Institutes of Health conducted in the United States that evaluated heterologous booster regimens of FDA-authorized COVID-19 vaccines. In this study, adults who had

completed primary vaccination with a Moderna COVID-19 Vaccine 2-dose series (N=151), a Janssen COVID-19 Vaccine single-dose (N=156), or a Pfizer-BioNTech COVID-19 vaccine 2-dose series (N=151) at least 12 weeks prior to enrollment and who reported no history of SARS-CoV-2 infection were randomized 1:1:1 to receive a booster dose of one of three vaccines: Moderna COVID-19 Vaccine, Janssen COVID-19 Vaccine, or Pfizer-BioNTech COVID-19 Vaccine. Neutralizing antibody titers, as measured by a pseudovirus neutralization assay using a lentivirus expressing the SARS-CoV-2 Spike protein with D614G mutation, were assessed prior to administration of the booster dose (Day 1) and after the booster dose (Day 15). A booster response to the Pfizer-BioNTech COVID-19 Vaccine was demonstrated regardless of which COVID-19 vaccine was used for primary vaccination. An overall review of adverse reactions reported following the Pfizer-BioNTech COVID-19 vaccine heterologous booster dose did not identify any new safety concerns as compared to adverse reactions reported following the Pfizer-BioNTech COVID-19 vaccine primary vaccination or homologous booster dose (FDA, 2022).

Recent studies indicate that additional doses in people who are moderately or severely immunocompromised are safe and can increase antibody response. Small studies in solid organ transplant recipients in Toulouse, Strasbourg, and Baltimore demonstrate immunogenicity of a 4th mRNA dose when administered 1–2 months after the 3rd dose (Kamar et al., 2021; Benotmane et al., preprint; Alejo et al., 2021). Multiple studies, including COV-BOOST and the NIH mix-and-match study demonstrated safety and immunogenicity of a booster dose in the general population when administered at intervals as short as 3 months following a 2-dose primary series (Munro et al., 2021; Atmar et al., preprint). Finally, multiple countries have implemented booster doses at least 3 months after primary vaccination in the general population (e.g., UK, Germany, Netherlands).

What is the available supporting evidence for a longer/extended interval (8 weeks) between the first and second dose in the mRNA vaccine primary series schedule?

New evidence suggests that an interval longer than 3 weeks between primary series doses may reduce the risk of myocarditis and result in greater immunogenicity and effectiveness, such that there may be greater benefits and fewer risks with this dosing interval; however, the benefit of delaying the second dose beyond an interval of 8 weeks may be limited.

Several studies provide evidence that indicate greater immunogenicity and VE following a longer interval between the first and second dose of the mRNA primary series.

- Neutralizing antibody titers were higher following an extended dosing (6-14 weeks) interval with mRNA vaccine, compared to a standard 3–4 week interval (Payne, 2021; Grunau, 2021; Amirthalingam, 2021; Parry, 2022).
- Among an observational cohort of SARS-CoV-2 infection naïve health care workers (n=334) in the United Kingdom, persons who received Pfizer-BioNTech COVID-19 Vaccine following an extended dosing interval (6–14 week) had higher neutralizing antibody titers and antigen-specific B cell responses 4 weeks after their second dose, compared to persons with a short interval (3–4 week) (Payne, 2021).
    - Investigators observed sustained B and T cell responses, noting that the longer interval between vaccine doses may promote efficient T cell expansion and long-term memory cell persistence (Payne, 2021).
- In a large test-negative design study to evaluate VE among adults aged ≥18 years in British Columbia and Quebec, Canada, two-dose mRNA VE against infection and hospitalization was significantly higher with a longer dosing interval (7–8 weeks vs. 3–4 weeks) (Skowronski, 2021). VE appeared to plateau at the 7–8 week interval.
- A test-negative case control study among adults aged 50–89 years in England demonstrated that Pfizer-BioNTech VE was higher with longer (>6 weeks) intervals compared to short (3–4 weeks) intervals for all age groups (Amirthalingam).

A longer interval between the first and second dose of mRNA vaccines may improve safety, especially for young men.

- In an unpublished (preprint) retrospective population-based cohort using Canada's provincial vaccine registry and passive vaccine safety surveillance between December 2020 and September 2021, reported rates of myocarditis/pericarditis among all persons were greater with shorter intervals (3–4 weeks) between dose 1 and dose 2 compared to extended intervals (≥8 weeks) for both Moderna (unadjusted rate ratio [RR]= 5.2, 95% CI 2.6–10.0) and Pfizer-BioNTech (RR=5.5, 95% CI 3.1–9.6) (Buchan, preprint).
- The lower reported rates of myocarditis/pericarditis among persons receiving their second vaccine dose at extended intervals (≥8 weeks) was observed across schedules of mRNA vaccine primary series (i.e., Pfizer-Pfizer, Moderna-Moderna, Pfizer-Moderna) (Buchan, preprint).

Countries such as Australia, Canada, Denmark, Finland, France, Germany, Norway, Taiwan, and the United Kingdom have recommended extended mRNA vaccine primary series dosing for all persons or specific sub-groups, based on their reviews of available immunological, safety, and effectiveness data, as well as the epidemiology of COVID-19, operational considerations, and other contextual factors.

What is the available supporting evidence for use of the COVID-19 vaccine by Pfizer for a second booster dose in people who have received a primary dose and first booster dose with Janssen COVID-19 Vaccine?
Real-world VE data from the use of COVID-19 vaccines in the U.S. have suggested that the Janssen COVID-19 Vaccine may have lower VE against both infection and severe disease compared to mRNA vaccines (IVY Network, 2021). Additionally, evidence is accumulating from observational studies in the U.S. to suggest individuals who have received Janssen COVID-19 Vaccine as both the primary vaccination and booster may have lower protection. In a recent study from CDC VISION network, VE against laboratory-confirmed COVID-19-associated emergency department and urgent care (ED/UC) encounters within 7-120 days since booster dose was 54% after 2 Janssen doses, 79% after 1 Janssen/1 mRNA dose, and 83% after 3 mRNA doses. VE estimates for the same vaccine regimens against laboratory-confirmed COVID-19-associated hospitalizations within 7-120 days since booster dose were 67%, 78%, and 90%, respectively (Natarajan et al., 2022).

What is the available supporting evidence for delaying the second primary dose in people who recently had SARS-CoV-2 infection by 3 months from symptom onset or positive test (if infection was asymptomatic)?
SARS-CoV-2 infection induces a robust humoral and cellular immune response (CDC, 2021). Additionally, a longer interval of at least 3 or 6 months between infection and vaccination may improve immune response by allowing time for the response to mature and avoiding interference from the vaccine (Abu-Raddad L, 2021; Zhong, 2021). Multiple large-scale studies have observed decreased risk of subsequent infection with antigenically similar variants by 80-93% for months after infection (CDC, 2021). Delaying vaccination for 3 months after infection may therefore help to maximize protection with minimal risk to the individual. However, robustness and duration of protection is variable (National Collaborating Center for Methods and Tools, 2021). The circulating variant, as well as individual-level factors such as age and comorbidities, can impact level of protection. For example, overall risk of reinfection increased during the Omicron wave, and protection from infection or vaccination, was less robust than against previous variants (Pulliam et al., 2022). Additionally, some populations (e.g., older adults, immunocompromised) may have decreased levels of protection following infection, necessitating an interval that balances the benefits and risks of delaying vaccination after infection at a population level.

Vaccination continues to be recommended regardless of the option for delaying vaccination after infection. Numerous immunologic studies and a growing number of epidemiologic studies have shown that vaccinating previously infected individuals significantly enhances their immune response and effectively reduces the risk of subsequent infection, including in the setting of increased circulation of more infectious variants (CDC, 2021).

What is the available supporting evidence for revaccination of people who received COVID-19 vaccine during B-cell-depleting therapy administered over a limited period?

Studies of people on B-cell-depleting therapies indicate patients do not achieve adequate seroconversion or have a decreased odds ratio of seroconversion if they were vaccinated during therapy (Haggenberg, 2022a; Haggenberg, 2022b).The timing of vaccination relative to therapy influences vaccine immunogenicity; vaccination at least 6 months after therapy has demonstrated improved seroconversion (Kornek, 2022; Schietzel, 2022, Disanto, 2021). The option to be revaccinated for people who received vaccination during therapy would allow the opportunity to develop a more sufficient immune response.

Risk-Benefit of the COVID-19 vaccine by Pfizer-BioNTech as Primary, Additional, and/or Booster Vaccination for Individuals Described in the EUI

The duration of vaccine-induced protection from primary vaccination with COVID-19 vaccines is unknown. Efficacy data from clinical studies of 2-dose primary series supported benefit of the COVID-19 vaccine by Pfizer-BioNTech in preventing severe COVID-19 and supported its FDA approval. Effectiveness of an additional primary dose of the COVID-19 vaccine by Pfizer-BioNTech is inferred from immunogenicity data in immunocompromised adults who received a single additional primary dose. Clinical trials demonstrated that relative vaccine efficacy was 95.3% (95% confidence interval: 89.5%, 98.3%) among persons aged 16 years and older who received a booster dose of the COVID-19 vaccine by Pfizer-BioNTech (administered predominantly between 10–12 months following completion of primary series) in the previous 2 months, compared to those who had only completed two primary doses. Rates of local or systemic adverse events in these trials were similar or lower after a booster dose than after the second primary dose (Perez, 2021; Gruber, 2021). Additionally, the real world data from the Ministry of Health of Israel that included over 6,300 individuals aged 12–15 years and over 4.1 million individuals aged 16 years and older who received a booster dose of the COVID-19 vaccine by Pfizer-BioNTech at least 5 months after primary vaccination revealed no new safety concerns.

Effectiveness of a heterologous booster dose of COVID-19 vaccine by Pfizer-BioNTech is inferred from data in adults who received a booster dose following primary vaccination with the Pfizer-BioNTech COVID-19 Vaccine or another FDA-authorized COVID-19 vaccine. Available data on the safety or efficacy of a Pfizer-BioNTech COVID-19 vaccine dose after receipt of a non-FDA authorized or approved COVID-19 vaccine are limited. However, based on available information, it appears reasonable to anticipate that known and potential risks of an additional primary dose or a booster dose of the COVID-19 vaccine by Pfizer-BioNTech may be outweighed by its likely benefit to enhance or restore protection by the primary vaccination, which might have waned over time, especially in people with immunocompromising conditions or taking immunosuppressive medications who may require a shorter interval for booster doses.

Refer to the CDC's Interim Clinical Considerations for Use of COVID-19 Vaccines for additional information.

Available Alternatives

Currently, the Pfizer-BioNTech COVID-19 vaccine and Moderna COVID-19 vaccine are the only FDA-approved vaccines for which EUI provide for primary, additional, and/or booster dose administration.

Reporting Adverse Event or Medication Errors

The vaccination provider is responsible for mandatory reporting of the following to the Vaccine Adverse Event Reporting System (VAERS):

- vaccine administration errors whether or not associated with an adverse event,
- serious adverse events (irrespective of attribution to vaccination),
- cases of Multisystem Inflammatory Syndrome (MIS) in adults and children, and
- cases of COVID-19 that result in hospitalization or death.

Complete and submit reports to VAERS online at https://vaers.hhs.gov/reportevent.html.
For further assistance with reporting to VAERS call 1-800-822-7967.

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