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## Booster Doses of COVID-19 Vaccines

**Revised 11/29/21:** This article originally went to press on 11/10/21. On 11/19/21 the FDA changed their recommendations. We have included a revision note to reflect these changes.

The FDA has expanded the Emergency Use Authorizations (EUAs) for the mRNA-based COVID-19 vaccines manufactured by Pfizer/BioNTech *(Comirnaty)* and Moderna *(Spikevax)* and the adenovirus-based vaccine manufactured by Johnson & Johnson/Janssen to include administration of a booster dose in select populations after primary immunization with either the same COVID-19 vaccine or a different one.

**RECOMMENDATIONS —** A single booster dose of any COVID-19 vaccine can now be administered ≥6 months after a primary series of an mRNA-based vaccine in adults who are ≥65 years old or at high risk for severe COVID-19 because of an underlying medical condition or frequent institutional or occupational exposure to SARS-CoV-2, or ≥2 months after a single primary dose of the Johnson & Johnson vaccine in any adult (see Table 1).[1,2] ***Revised***: As of November 19, 2021, the FDA has expanded the EUAs for the mRNA-based COVID-19 vaccines (*Comirnaty* and *Spikevax*) to include administration of a booster dose for all adults ≥18 years old after primary immunization with either the same COVID-19 vaccine or a different one.[19]

**DOSAGE —** The booster dose is the same as the dose for primary immunization for both *Comirnaty* (30 mcg [0.3 mL] IM) and the Johnson & Johnson vaccine ($5x10^{10}$ viral particles [0.5 mL] IM); it is half the dose for primary immunization for *Spikevax* (50 mcg [0.25 mL] vs 100 mcg [0.5 mL] IM).[3-5]

**CLINICAL STUDIES — Waning Immunity –** In a retrospective cohort study of ~3.4 million persons ≥12 years old in the US, those who received two doses of *Comirnaty* were significantly less likely to be infected with SARS-CoV-2 than those who were not vaccinated, but the relative risk reduction associated with vaccination declined from 88% at ≤1 month to 47% at ≥5 months after the second dose. Vaccination was also associated with a lower risk of hospitalization due to COVID-19; the relative risk reduction did not change significantly over time (87% at ≤1 month; 88% at ≥5 months).[6]

In a study in Israel that examined positive PCR test results for SARS-CoV-2 infection over 3 weeks in July 2021, adults ≥60 years old who completed a 2-dose primary series of the Pfizer/BioNTech vaccine in the second half of January 2021 had a significantly higher rate of infection than those who completed their series in the second half of March 2021 (3.3 vs 1.7 cases/1000 persons). Similarly, adults ≥60 years old who completed their series in January had a significantly higher rate of severe COVID-19 than those who completed it in March (0.34 vs 0.15 cases/1000 persons).[7]

In a US study of breakthrough infection rates between July 1 and August 27, 2021 in ~26,000 adults who had received primary immunization with *Spikevax*, the rate in an earlier-vaccinated (median 13 months since first dose) cohort was 36.4% higher than that in a later-vaccinated (median 8 months since first dose) cohort (77.1 vs 49.0 cases/1000 person-years).[8]

The efficacy of the Johnson & Johnson vaccine appears to be sustained through at least 6 months post-dose, but the peak efficacy of a single Johnson & Johnson dose seems to be lower than that of a 2-dose primary series of an mRNA-based vaccine.[9-11]

**Booster Immunogenicity –** Longitudinal immunogenicity studies (unpublished; summarized in FDA Fact Sheets) compared titer levels of anti-SARS-CoV-2 neutralizing antibodies after a booster dose to those achieved after completion of primary immunization in adults with no evidence of prior SARS-CoV-2 infection. In 210 adults 18-55 years old who received a booster dose of *Comirnaty* about 6 months after completion of a 2-dose primary series, the geometric mean titer (GMT) 1 month after the booster dose was 3.29-fold higher than it was 1 month after the second primary-series dose.[3] In 149 adults

**Table 1. Indications and Dosage Regimens for COVID-19 Vaccines[1]**

| Indication | Pfizer-BioNTech *(Comirnaty)* | Moderna *(Spikevax)* | Johnson & Johnson/Janssen |
|---|---|---|---|
| Primary immunization | ≥16 yrs: 30 mcg (0.3 mL) IM at 0 and 3 weeks<br>12-15 yrs: 30 mcg (0.3 mL) IM at 0 and 3 weeks | ≥18 yrs: 100 mcg (0.5 mL) IM at 0 and 4 weeks | ≥18 yrs: $5x10^{10}$ vp (0.5 mL) IM once |
| Additional primary dose for immunocompromised persons | ≥12 yrs: 30 mcg (0.3 mL) IM ≥4 weeks after second primary dose | ≥18 yrs: 100 mcg (0.5 mL) IM ≥4 weeks after second primary dose | N.A. |
| Booster dose in at-risk adults[2] after a Pfizer-BioNTech or Moderna primary series[3] | 30 mcg (0.3 mL) IM ≥6 months after last primary dose | 50 mcg (0.25 mL) IM ≥6 months after last primary dose | $5x10^{10}$ vp (0.5 mL) IM ≥6 months after last primary dose |
| Booster dose in adults after a Johnson & Johnson primary dose | 30 mcg (0.3 mL) IM ≥2 months after primary dose | 50 mcg (0.25 mL) IM ≥2 months after primary dose | $5x10^{10}$ vp (0.5 mL) IM ≥2 months after primary dose |

N.A. = not authorized; vp = viral particles
1. The Pfizer-BioNTech vaccine has received full FDA licensure for use as a 2-dose primary series in patients ≥16 years old. All other recommendations are based on FDA Emergency Use Authorizations (EUAs).
2. Aged ≥65 years or at high risk for severe COVID-19 because of an underlying medical condition or frequent institutional/occupational exposure to SARS-CoV-2.
3. After either a 2- or 3-dose primary series. CDC. Considerations for use of a COVID-19 vaccine booster dose. October 25, 2021. Available at: https://bit.ly/3EnjXZ8. Accessed October 29, 2021.

who received a 50-mcg booster dose of *Spikevax* ≥6 months after completion of a 2-dose primary series, the GMT 4 weeks after a 50-mcg booster dose was 1.8-fold higher than it was 4 weeks after the second primary-series dose.[5] In 38 adults who received a booster dose of the Johnson & Johnson vaccine 12 weeks after a primary dose, the GMT 4 weeks after the booster dose was 1.6-fold higher than it was 4 weeks after the primary dose.[4]

**Booster Efficacy –** In a one-month cohort study in ~1.1 million Israeli residents who had completed a 2-dose primary series of the Pfizer/BioNTech vaccine ≥5 months previously, persons who received a booster dose had significantly lower rates of SARS-CoV-2 infection (by 11.3-fold) and severe COVID-19 (by 19.5-fold) beginning 12 days after administration compared to those who did not.[12] In a follow-up analysis, relative reductions in the rates of symptomatic and severe COVID-19 associated with booster immunization persisted through ~2 months after the booster dose, and among persons ≥60 years old, the rate of death due to COVID-19 was 14.7-fold lower beginning 12 days after administration in patients who received a booster dose than it was in those who did not receive one.[13]

In an unpublished double-blind trial (ENSEMBLE 2; summarized in an FDA presentation), 31,300 persons were randomized to receive two doses of the Johnson & Johnson vaccine or placebo 8 weeks apart. After a median follow-up of 36 days, the vaccine efficacy rate for prevention of moderate to severe COVID-19 from 14 days after the second dose, the primary endpoint, was 75% (94% in the US). There were no cases of severe or critical COVID-19 in vaccine recipients versus 8 in the placebo group. This data analysis was performed in June 2021, before the Delta variant of SARS-CoV-2 became predominant in the US.[11]

**Heterologous ("Mix-and-Match") Boosters –** In an unpublished nonrandomized trial (summarized in an FDA presentation), 458 adults who had received primary immunization with one of the three FDA-authorized COVID-19 vaccines ≥12 weeks previously were given a booster dose of either the same vaccine or one of the two other vaccines (for *Spikevax*, 100-mcg rather than 50-mcg booster doses were used). For all vaccine combinations, the GMT of anti-SARS-CoV-2 neutralizing antibodies increased significantly in the 2 weeks after the booster dose.[14]

**ADVERSE EFFECTS —** Adverse effects with a third dose of an mRNA-based COVID-19 vaccine appear to be similar to those with the second primary-series dose.[15] Lymphadenopathy occurs more frequently with a booster dose. Booster immunization with mRNA-based COVID-19 vaccines has not been associated with increased rates of hypersensitivity reactions, Bell's palsy, or myocarditis/pericarditis compared to primary immunization.[16,17]

Adverse effects with a booster dose of the Johnson & Johnson vaccine appear to be similar to those with the primary dose. Booster immunization has not been associated with a higher rate of thrombosis with thrombocytopenia syndrome (TTS) compared to primary immunization with the vaccine. In the UK, the rate of TTS with the second dose of the

adenovirus-based COVID-19 vaccine manufactured by AstraZeneca (not authorized for use in the US) has been lower than the rate with the first dose.[11,18]

No vaccine-related serious adverse effects were reported in the heterologous booster trial. Adverse effects with heterologous and homologous booster immunization appear to be similar.[14]

**CONCLUSION** — Booster immunization has been associated with decreased rates of SARS-CoV-2 infection and severe COVID-19. The FDA has authorized use of a single booster dose of a COVID-19 vaccine in certain adults who received a primary series with the Pfizer-BioNTech vaccine *(Comirnaty)* or the Moderna vaccine *(Spikevax)* ≥6 months previously and in all adults who received a primary dose of the Johnson & Johnson/Janssen vaccine ≥2 months previously. The vaccine used for the booster dose can be different from the one used for primary immunization. ■


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