ACIP Evidence to Recommendations for Use of COVID-19 Vaccine Booster Doses

Question:

- Pfizer-BioNTech:
  - Should persons aged ≥65 years and residents of long-term care facilities receive a Pfizer-BioNTech COVID-19 vaccine?
  - Should adults 18–64 years of age at risk for severe COVID-19 due to underlying medical conditions or at risk of SARS-CoV-2 exposure due to occupation/setting receive a Pfizer-BioNTech COVID-19 vaccine booster dose?
- Moderna: Among risk groups for whom CDC recommends a Pfizer-BioNTech booster dose, should those who received a Moderna COVID-19 vaccine primary series be recommended to receive a single booster dose ≥6 months after completion of the primary series?
- Janssen: Among people aged ≥18 years who received Janssen COVID-19 vaccine for their primary COVID-19 vaccine, should a single booster dose be recommended ≥2 months after receipt of the initial dose?

Population:

- Pfizer-BioNTech: Persons aged ≥18 years who completed a Pfizer-BioNTech COVID-19 vaccine primary series ≥6 months ago
- Moderna: Persons aged ≥18 years who completed a Moderna COVID-19 vaccine primary series ≥6 months ago
- Janssen: Persons aged ≥18 years who completed a Janssen COVID-19 vaccine primary series ≥2 months ago

Intervention:

- Pfizer-BioNTech COVID-19 vaccine booster dose (30 µg)
- Moderna COVID-19 vaccine booster dose (50 µg)
- Janssen COVID-19 vaccine booster dose ($5X10^{10}$ viral particles)

Comparison: No booster dose

Outcomes:

- Symptomatic laboratory-confirmed COVID-19
- Hospitalization due to COVID-19
- Death due to COVID-19
- Transmission of SARS-CoV-2 infection
- Serious adverse events
- Reactogenicity

Background: The emergence of SARS-CoV-2, the virus that causes coronavirus disease 2019 (COVID-19), has led to a global pandemic with substantial societal and economic impacts on individual persons and communities. In the United States, more than 45 million cases and more than 700,000 COVID-19-associated deaths have been reported as of October 20, 2021. Persons of all ages are at risk for infection and severe disease. However, the risk for severe illness from COVID-19 is higher in people aged ≥65 years, those living in long-term care facilities, and those with chronic medical conditions. In addition, persons in certain occupational groups, such as healthcare personnel, or institutional settings, such as correctional facilities or homeless shelters, are at increased risk for SARS-CoV-2 exposure and transmission.

Three COVID-19 vaccines are currently approved under a Biologics License Application or authorized under an Emergency Use Authorization (EUA) by the Food and Drug Administration (FDA) and recommended for primary vaccination by the Advisory Committee on Immunization Practices (ACIP): the two-dose mRNA-based Pfizer-BioNTech/Comirnaty and Moderna COVID-19 vaccines and the single-dose adenovirus vector-based Janssen (Johnson & Johnson) COVID-19 vaccine.

During September-October, 2021, the FDA amended the COVID-19 vaccine EUAs to allow for booster doses of Pfizer-BioNTech, Moderna, or Janssen COVID-19 in persons who completed primary vaccination with these vaccines, as well as use of each of the available COVID-19 vaccines as a heterologous (or "mix and match") booster dose in eligible individuals following completion of primary vaccination with a different COVID-19 vaccine.

Additional background information supporting the ACIP recommendation on the use of additional or booster doses of COVID-19 vaccine can be found in the relevant publication of the recommendation referenced on the ACIP website.

Problem

Criteria	Evidence	Additional Information
Is the problem of public health importance?	COVID-19 is a major global public health threat that dramatically disrupted all sectors of society worldwide. In the United States, COVID-19 has important associated morbidity and mortality. **Incidence:** As of October 20, 2021, there were 45,070,875 COVID-19 cases reported in the United States for an incidence of 13,576 cases per 100,000 population.[1] **Hospitalization:** COVID-19-associatiated hospitalization rates were 9-15 times higher in unvaccinated adults compared to fully vaccinated adults.[2,3] **Mortality:** As of October 20, 2021, there were 728,125 COVID-19-associated deaths reported in the United States.[4] **Vaccine effectiveness:** Reductions in VE of an mRNA COVID-19 vaccine primary series against SARS-CoV-2 infection have been observed in the context of waning immunity and emergence of the Delta variant in the United States, including among groups recommended to receive early vaccine doses[5]: 75% (95% CI: 60–85%)[6] to 84 % (95% CI: 83–86%)[7] among adults aged ≥65 years, 53% (95% CI: 49–57%)[8] among residents of long-term care facilities, and 66% (95% CI: 26–84%)[9] among healthcare personnel and other frontline workers[5] during the Delta period. VE of an mRNA COVID-19 vaccine primary series against COVID-19-associated hospitalization overall remains high across groups during the Delta period (78% [95% CI: 62–87%][10] to100% [96–100%])[6], although some studies show a slightly lower VE against hospitalization in older adults. Although data are limited, some studies suggest stable VE of Janssen vaccine over time; however, VE estimates range from 58% (95% CI: 12–80%)[11] to 83% (95% CI: 61–93%)[12] against SARS-CoV-2 infection and 60% (95% CI: 31–77%)[13] to 83% (95% CI: 61–93%)[12] against COVID-19-associated hospitalization.	**Vaccination:** As of October 20, 2021, more than 189 million people in the United States are fully vaccinated against COVID-19.[14] Among these, approximately 55% received Pfizer-BioNTech, 37% received Moderna, and 8% received Janssen.[14] **Variants of Concern:** As of October 20, 2021, the Delta variant is the dominant circulating variant in the United States and is more than twice as contagious as previous variants.[15]

Benefits and Harms

Criteria Criteria	Evidence Evidence	Additional Additional Information Information
How substantial are the desirable anticipated effects?	Because data on the critical GRADE outcome of prevention of symptomatic COVID-19 was not available for all vaccines, benefit of a booster dose was inferred through immunogenicity. Compared with at 1 month after the last dose in the primary series, geometric mean ratios of neutralization titers were 1.8–3.3-fold higher 1 month after a homologous mRNA COVID-19 vaccine booster dose administered 6 months after completing the primary series and spike binding antibody titers were 4.6–12 fold higher after a homologous Janssen COVID-19 booster dose administered 2–6 months after completing primary vaccination. One clinical trial found that homologous or heterologous booster dose administration, in which participants received either a Pfizer-BioNTech, Moderna, or Janssen COVID-19 vaccine primary series followed by a booster dose of the same or a different vaccine, resulted in neutralizing antibody titers that were similar or higher than those observed following homologous booster vaccination. Observational studies from Israel demonstrated short-term incremental VE of a booster dose (compared to second dose) of Pfizer-BioNTech vaccine that ranged from 70% (95% CI: 62–76%) in persons aged ≥40 years to 91.2% (95% CI: 90.0–91.9%) in persons aged ≥60 years (7). In the U.S. study population, efficacy of the Janssen vaccine against moderate-to-severe/critical COVID-19 at least 14 days after vaccination was 93.7% (95% CI: 58.5%–99.9%) for 2 doses administered 2 months apart versus 74.4% (95% CI: 65.0–81.6%) for a single dose.	
How substantial are the undesirable anticipated effects?	In clinical trials for mRNA and Janssen COVID-19 booster doses, rates of local or systemic adverse events were similar or less frequent after a booster dose than after the last dose of primary vaccination. No serious adverse events (SAEs) related to the vaccine were reported for mRNA booster doses; For Janssen, 3 SAEs (facial paresis, pulmonary embolism, and cerebrovascular accident) were attributed to booster doses within 6 months of administration, among 5,070 booster recipients in the evaluable population.	As of October 20, 2021, more than 11 million people had received an additional or booster dose in the United States and no unexpected patterns of adverse events have been observed in national safety surveillance systems. Risk of serious adverse events of myocarditis, thrombosis with thrombocytopenia syndrome, and Guillain-Barré syndrome after a COVID-19 vaccine booster dose are not well understood.
Do the desirable effects outweigh the undesirable effects?	The Work Group concluded that the desirable effects of a COVID-19 booster vaccine dose outweigh the undesirable effects for the populations under consideration for a booster dose.	

Criteria	Evidence	Additional Information
What is the overall certainty of this evidence for the critical outcomes?	Level of certainty was type 4 for: • Prevention of symptomatic COVID-19 • Prevention of hospitalization due to COVID-19 (Pfizer-BioNTech, Janssen) • Prevention of death due to COVID-19 (Janssen) • Serious adverse events • Reactogenicity No data were available to assess the other important GRADE outcome of prevention of transmission of SARS-CoV-2 infection. See GRADE tables for additional information: https://www.cdc.gov/vaccines/acip/recs/grade/covid-19-booster-doses.html.	

Values

Criteria	Evidence	Additional Information
Does the target population feel that the desirable effects are large relative to undesirable effects?	In published surveys completed in August (n=5), 76%-87% of vaccinated adults reported they would get a booster dose, if available.[1-5] In one survey, this increased to 93% of surveyed adults if it was recommended by their primary care provider. In an unpublished survey conducted in August 2021, 6364% of vaccinated respondents said they would get a COVID-19 vaccine booster as soon as possible. Respondents also stated that older adults, long-term care facility residents, and healthcare personnel should be prioritized for booster doses.	Knowledge and attitudes may change with time, and intentions may not reflect uptake. The survey sample populations may not be representative, limiting the generalizability of the results to all adults in the U.S. Furthermore, the surveys sampled a broader group of individuals than those that are under consideration for a booster dose.

Acceptability

Criteria	Evidence	Additional Information
Is the intervention acceptable to key stakeholders?	COVID-19 vaccination has been implemented in a variety of situations, including state and local health departments, healthcare sites and hospitals, mass vaccination clinics, long term care facilities, and retail pharmacies. As of October 20, 2021, more than 410 million COVID-19 doses have been administered, including 11 million additional or booster doses, suggesting that COVID-19 booster vaccination will likely be acceptable to key stakeholders.[1]	

Resource Use

Criteria	Evidence	Additional Information

Criteria	Evidence	Additional Information
Is the intervention a reasonable and efficient allocation of resources?	All COVID-19 vaccines, including booster doses, will be provided free of charge to the U.S. population. However, health systems or health departments could incur costs for vaccination program planning and implementation. Fees for administration of COVID-19 vaccines recommended by ACIP are reimbursable by insurance or other federal programs.	The Work Group concluded that cost-effectiveness may not be a primary driver for decision-making on this policy question. The Work Group also stressed the importance of ensuring global equity in access to COVID-19 vaccines for the primary series, while the U.S. pursues booster vaccination.

Equity

Criteria	Evidence	Additional Information
What would be the impact of the intervention on health equity?	Persons belonging to certain racial and ethnic groups are at greater risk for COVID-19 as well as less likely to receive COVID-19 vaccination. As of October 16, 2021, cumulative COVID-19 associated hospitalizations in the United States illustrated that rates (per 100,000 population) were higher among American Indian/Alaska Native, Black, and Hispanic populations compared to White and Asian/Pacific Islander populations.[1] Further analysis showed that Hispanic or Latino, Black, American Indian or Alaska Native (AI/AN), and Native Hawaiian or Other Pacific Islander (NH/PI) populations in the United States experienced higher rates of COVID-19 infection and mortality compared with the non-Hispanic White population and greater excess mortality (i.e., the percentage increase in the number of persons who have died relative to the expected number of deaths for a given place and time).[2] During the COVID-19 pandemic in 2020, the highest total excess mortality incidence rate among adults aged 25-64 years were among American Indian/Alaska Native populations, followed by Black, Native Hawaiian or Other Pacific Islander and Hispanic populations respectively. [2] Vaccination coverage data demonstrate that racial and ethnic disparities in vaccine uptake are narrowing; however, the proportion of Black and Hispanic persons who are fully vaccinated against COVID-19 is lower than for persons of other racial and ethnic minority groups.[3] However, vaccine effectiveness estimates do not vary by race and ethnicity. In one study, among persons aged ≥50 years, VE against hospitalization was[4]: • Overall: 89% (95% CI: 87-91%) • Black individuals: 86% (95% CI: 75-92%) • Hispanic individuals: 90% (95% CI: 85-93%)	

Feasibility

Criteria	Evidence	Additional Information

Criteria	Evidence	Additional Information
Is the intervention feasible to implement?	To date, over 410 million COVID-19 vaccine doses have been administered in the United States, demonstrating that the vaccine is feasible to implement. In addition, from August 13, 2021-October 20, 2021, 11.2 million individuals have received an additional or booster dose.[1] Booster doses will be given in a variety of settings: pharmacies, providers offices, health departments, occupational clinics, and federal programs (e.g., LTCF program). Over 70% of current COVID-19 vaccine administration occurs in pharmacies.[2] However, there are several factors that could negatively affect vaccine implementation: • Dosage for the Moderna booster dose is half of the dose used for primary series[3]; education of vaccinators is necessary to help prevent vaccination errors • Jurisdictions are balancing multiple issues: surge in COVID-19 cases, outreach to unvaccinated individuals to receive primary vaccination, preparing for pediatric COVID-19 vaccination, and preparing for influenza vaccination campaigns.	

Balance of consequences

Desirable consequences *outweigh* undesirable consequences in most settings.

Is there sufficient information to move forward with a recommendation? Yes.

Policy options for ACIP consideration

- ACIP recommends the intervention
- ACIP recommends the intervention based on individual risks and benefits

Draft recommendation: ACIP and CDC recommendations

mRNA COVID-19 vaccine (Pfizer-BioNTech, Moderna) recipients:

The following recipients of an mRNA primary series should receive a single COVID-19 vaccine booster dose at least 6 months after completion of the primary series:

- People aged 65 years and older
- Residents aged 18 years and older in long term care settings
- People aged 50–64 years with certain underlying medical conditions

The following recipients of an mRNA primary series may receive a COVID-19 vaccine booster dose at least 6 months after completing their primary series based on their individual risks and benefits:

- People aged 18–49 years with certain underlying medical conditions
- People aged 18–64 years at increased risk for SARS-CoV-2 exposure and transmission because of occupational or institutional setting*

Any FDA-approved or authorized COVID-19 vaccine (Pfizer-BioNTech, Moderna, or Janssen) can be used as the booster dose, at an interval of at least 6 months since primary vaccination.

Janssen COVID-19 vaccine

Persons aged 18 years and older who received primary vaccination with Janssen COVID-19 vaccine should receive a single COVID-19 vaccine booster dose at least 2 months later. Any FDA-approved or authorized COVID-19 vaccine (Pfizer-BioNTech, Moderna, or Janssen) can be used as the booster dose, at an interval of at least 2 months since the primary Janssen vaccine dose.

* ACIP voted 9–6 against an interim recommendation for use of a single Pfizer-BioNTech COVID-19 vaccine booster dose, based on individual benefit and risk, for persons aged 18–64 years who are in an occupational or institutional setting where the burden of COVID-19 infection and transmission are high, at least 6 months after a Pfizer-BioNTech primary series under the FDA's EUA. The CDC Director did not approve the committee's recommendation and made a CDC recommendation that persons aged 18–64 at high risk for COVID-19 exposure and transmission because of occupational or institutional setting may receive a Pfizer-BioNTech COVID-19 booster dose at least 6 months after a Pfizer-BioNTech primary series under the FDA's EUA.

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Problem:

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Feasibility:

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